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

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Abstract

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

Study design—A predetermined sample size of 64 ELBW infants, between 10 to 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 MRI was performed at 38 weeks postmenstrual age; brain tissue regions were segmented and quantified automatically with a high degree of accuracy and nine structures were segmented manually. All analyses of regional brain volumes were adjusted by postmenstrual age at MRI scan.

Results—The study groups were similar at baseline and eight 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 $\pm$ 40.3 cm³ and 277.8 $\pm$ 59.1 cm³, respectively (adjusted mean difference: 6.35 cm³ (95% CI: (–20.8, 32.5); P=0.64). Three of the 31 hydrocortisone treated infants and five of the 33 placebo treated infants survived without severe BPD (RR 0.62, 95% CI: 0.13, 2.66; P=0.49). 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.

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The authors declare no conflicts of interest.

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 NICU discharge.

Keywords

Bronchopulmonary dysplasia; corticosteroids; extremely low birth weight; magnetic resonance imaging; brain injury; mechanical ventilation

Bronchopulmonary dysplasia (BPD), an inflammatory disease of arrested lung development in extremely low birth weight (ELBW; BW < 1000g) 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 one 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 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 (birth weight: < 1000 g) infants in the Neonatal ICU 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 $\times$ FiO₂) was $\leq$ 2.0 and stable or increasing or if the respiratory index score was $\leq$ 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 (NCT00167544).

Randomization was stratified by birth weight (< 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 two study pharmacists. An independent study

monitor (W. Carlo) 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) 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, one 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 BP >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 acceptable 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 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 NIH Consensus definition of BPD was used; severe BPD was defined as oxygen treatment for at least 28 days plus physiologic need for 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 four 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 after feeding, during natural sleep whenever possible (90% unsedated). Axial PD/T2w scans were used for volumetry with TE 15/175 ms; TR 10000 ms; FOV 18x18 cm; matrix 512x512; voxel dimensions: 0.36Hx0.36Wx1.98D 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, MN) 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 to 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 difference equates to a 2-week growth in brain size.¹⁵ This sample size also provides 80% power to detect a difference of 11 days on positive pressure support or larger. An intention-to-treat analysis was performed. The primary analysis of total brain tissue volume was performed using multiple linear regression controlling for postmenstrual age at MRI scan (centered to the mean postmenstrual age at MRI from both groups) to adjust for differences in timing at MRI. The distributions of potentially important confounding variables at baseline were compared in the two groups using parametric and non-parametric tests for continuous and categorical data as appropriate. In secondary analyses, small group differences that were found in three baseline variables were adjusted using multiple regression analyses. Regression diagnostics were performed to verify assumptions of regression testing. Secondary hypotheses were assessed using t-tests or rank order tests for continuous dependent variables and Chi-square tests or Fisher exact tests for categorical outcomes. Censored regression Tobit model was used to compare the days on positive pressure ventilation (and supplemental oxygen) between groups.

To avoid bias from differential deaths between groups in evaluating brain volume outcomes, we planned to assign the worst outcome (eg, lowest brain tissue volume) to those who died before discharge MRI and retain all subjects in the analyses. Otherwise, if hydrocortisone did not affect mortality, we planned to exclude such infants from primary and secondary brain volume analyses. No adjustment for multiple comparisons was performed. Two-sided P values of less than 0.05 were considered to indicate statistical significance. All analyses were performed using STATA 11.0 (College Station, TX).

RESULTS

ELBW infants (n=64) were enrolled between October 11, 2005 and September 8, 2008 (Figure). These infants were extremely immature and at very high risk for BPD; mean (SE) birth weight was 665 (16) grams, median (IQR) gestational age was 25 (24 – 26) completed weeks, and respiratory index score was 4.2 (3.1 – 5.7). The two groups were similar with respect to baseline demographic and clinical characteristics of the mothers and infants (Table I). One hydrocortisone-treated and two placebo-treated infants received high frequency ventilation at the time of randomization and the rest were supported with conventional ventilation.

The median age at trial entry was 16 days of age for the placebo group and 17 days for the hydrocortisone group. Brain MRI was obtained at a mean (SE) postmenstrual age of 38.9 (0.55) weeks in the hydrocortisone group and 40.2 (0.75) weeks in the placebo group (P=0.15). All adjusted volumes were centered at 39.6 weeks, the mean postmenstrual age at MRI for both groups. The analyses included one infant in the hydrocortisone group whose parents decided to withdraw her from the treatment protocol after the fourth study dose. Four surviving infants in the placebo arm could not be analyzed for the primary or secondary brain volume outcomes because of early transfer back to referral hospital, inability to perform MRI within study window (n=2), and poor image quality. Secondary structural volumes could not be determined in one hydrocortisone and two placebo treated infants due to excessive motion artifacts. Total tissue volume measurement however was possible using manual segmentation in these three infants.

Study Intervention and Co-Interventions

All study infants received the correct allocation of study drug at the intended dose. No infant had doses held or reduced due to suspected steroid toxicity. No infants were given indomethacin during the 7-day intervention period. Six infants in the hydrocortisone (19%) and seven in the placebo group (21%) received postnatal corticosteroids after study drug completion ($P=0.85$). Six infants (2 in the hydrocortisone group and 4 in the placebo group) received dexamethasone for ventilator-dependent BPD and five infants (3 in the hydrocortisone group and 2 in the placebo group) received hydrocortisone for suspected adrenal insufficiency.

Outcomes

An equal number of infants died ($n=8$) in each treatment arm prior to brain MRI outcome assessment. The mean adjusted (for postmenstrual age at MRI) total tissue volume in the hydrocortisone-treated infants was 277.8 cm^3 and 271.5 cm^3 in the placebo-treated infants, values that were not different (Table II). Pre-specified secondary outcomes of regional volumes of the cerebral white matter, cortical gray matter, cerebrospinal fluid, cerebellum, hippocampi, and subcortical gray matter, were also comparable between the two study groups. In exploratory analyses, several other brain structural volumes were examined and also found to be unaffected by hydrocortisone administration (Table II). In secondary analyses, adjusting for small baseline differences in exposure to antenatal steroids, sex, and baseline respiratory index score did not influence regional volume differences (Table II). Intraventricular/parenchymal hemorrhage within the first 28 days of life on cranial ultrasound was observed in 29.0% (9/31) of hydrocortisone treated and 39.4% (13/33) placebo-treated infants. White matter injury, defined as cystic periventricular leukomalacia, porencephalic cyst, parenchymal hemorrhage, and/or ventriculomegaly on brain MRI and/or ultrasound closest to 36 weeks postmenstrual age was noted in 16.1% (5/31) of hydrocortisone treated and 30.3% (10/33) of placebo treated infants.

Respiratory secondary outcomes at 36 weeks postmenstrual age, including survival without severe BPD, days on positive pressure support, and days on supplemental oxygen were also not significantly different in unadjusted and adjusted analyses (Table III). One placebo and two hydrocortisone-treated infants were extubated from mechanical ventilation during or within one day following completion of the 7-day study course.

Head circumference, weight, and length at 36 weeks postmenstrual age were no different between hydrocortisone and placebo treated infants (Table IV; available at www.jpeds.com). Risks of adverse events during and after hydrocortisone administration were closely examined. No significantly increased risk of intestinal perforations, necrotizing enterocolitis, proven bacterial infections, hyperglycemia, or hypertension was observed.

DISCUSSION

In this exploratory pilot randomized placebo-controlled trial, we observed neither significant short-term beneficial nor harmful effects of low dose hydrocortisone after the first week of age in high-risk ventilator-dependent ELBW infants. In order to optimize benefit to risk,⁵ we studied treatment doses that were 25–50% higher than doses in the four previous hydrocortisone prophylaxis trials and restricted enrollment to the highest risk infants after a week of age.^{16,17,18,19} Nevertheless, a cumulative dose of 17 mg/kg of systemic hydrocortisone administered over seven days had no discernible effect on pre-discharge respiratory morbidity or regional brain volumes. Despite the pulmonary benefits reported by three small pilot trials^{16,18,19} and one observational study,²⁰ two larger trials^{17,21} and a recent meta-analysis¹⁰ of all hydrocortisone trials did not show higher extubation rates or

improved survival without BPD. Enrollment of infants at relatively lower risk for BPD and use of lower dose hydrocortisone (13.5 mg/kg cumulative) may have contributed to lack of efficacy. A two-fold increased risk of spontaneous intestinal perforations following randomization to early hydrocortisone was observed in a recent meta-analysis, however this complication was primarily observed in infants on concomitant indomethacin therapy.^{10,16,17,18} In our trial, two hydrocortisone treated, but none from the placebo treated infants developed spontaneous intestinal perforation ($P=0.23$).

Pre-discharge pulmonary benefits have been reported in one observational study of 25 ventilator-dependent preterm infants following higher dose hydrocortisone (72.5 mg/kg cumulative),²⁰ with absence of structural and functional neurologic adverse effects in larger groups of non-randomized hydrocortisone treated infants.^{22,23,24,25} Efficacy and safety of using such higher doses however has not been validated by other groups, especially following randomization. One recent observational study reported cerebellar volume deficits in preterm infants treated with much lower doses (cumulative median <14 mg/kg) of hydrocortisone.²⁶ Even if all potential measured confounders were adequately controlled in statistical analyses, lack of randomization in observational studies may result in baseline group imbalance in unmeasured confounders. Using a randomized trial design, we did not detect any adverse effects on cerebellar growth with lower doses of hydrocortisone. Our study provides the only evidence to date on the effects of corticosteroids on brain tissue and regional structural volumes in randomized high-risk preterm infants. This evidence is consistent with two randomized trials of hydrocortisone that did not observe any neurodevelopmental harm at 18 to 22 month corrected age,^{27,28} rather, the largest trial reported lower frequency of cognitive delays following hydrocortisone treatment in secondary analyses.²⁷

Two randomized trials of low dose dexamethasone (0.89 mg/kg cumulative) reported acute reduction in respiratory support but no effect on survival without BPD and comparable neurodevelopmental outcomes than placebo treated ELBW infants at 18 to 22 months corrected age.^{13,29,30} Safety however still cannot be adequately assured for either low dose dexamethasone or hydrocortisone because of the small number of infants studied and the lack of school age outcomes reported in randomized infants. Despite the lack of clear efficacy with hydrocortisone and observed neurotoxicity with dexamethasone, hydrocortisone use has increased from 1.1% in 1997 to 6.5% in 2006, and dexamethasone use, although decreased, remains at 6.8% nationally, based on data from the Pediatric group.³¹ Our pilot trial results do not support the use of low dose hydrocortisone in high-risk infants for BPD prevention.

Evaluation of hydrocortisone's effect on total and regional brain volumes was a novel strength of our trial. The primary outcome of total tissue volume was measured accurately and objectively using an automated program in order to minimize measurement error.¹⁴ Regional brain volumes appear to be exquisitely sensitive to dexamethasone's neurotoxic effects^{6,7} and correlate directly with working memory and neurodevelopmental impairments.^{7,32} Pre-discharge brain volumes may provide a more sensitive, accurate, and objective assessment of neurological effects of corticosteroids than cranial ultrasound or anatomic MRI. Additional study strengths include use of a respiratory risk score to enroll the highest risk infants and infrequent use of open label corticosteroids.^{10,11}

Our study had certain limitations. The trial was powered to show a difference in total brain tissue volume, equivalent to two weeks of brain growth or greater¹⁵ and not differences in death or BPD or neurodevelopmental outcomes. Although the comparable regional volumes and pulmonary outcomes suggest a lack of efficacy with lower dose hydrocortisone, only studies adequately powered to detect differences in BPD and/or neurodevelopmental

outcomes can validate our pilot observations. Regional brain volumes require further validation as robust surrogate outcome measures for neurodevelopmental impairment. It is possible that we did not capture the effect of hydrocortisone on brain volumes because a two-week growth difference may not be evident until after term-equivalent age. Additionally, the total tissue volumes in this trial were considerably smaller than the hypothesized volumes derived from Huppi et al.¹⁵ Their study sample consisted of healthy, appropriate for gestational age, more mature preterm infants. These characteristics were in stark contrast to our more immature, sicker, and smaller (large proportion of small for gestational age) ELBW infants, potentially explaining the smaller total and regional brain volumes in our subjects. Nutritional deficiency or intolerance with subsequent poor growth (~1.8 kg at 36 weeks postmenstrual age in both groups) may have also contributed to diminished group differences in brain volumes. The hydrocortisone regimen we used may not have been potent enough for the higher risk ventilator-dependent infants we selected, as evidenced by the high baseline respiratory index score, respiratory support at 36 weeks postmenstrual age, and mortality of study subjects.^{5,10,13} The hydrocortisone regimen we used is equivalent to one-half to two-thirds that of the two lower dose dexamethasone trials^{13,29} and one-fifth that of dexamethasone trials shown to reduce BPD.³

In this pilot trial, low dose systemic 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 NICU discharge. Our findings are consistent with findings from prior hydrocortisone trials and have implications for the design and conduct of future hydrocortisone trials, particularly for the selection of patient population and drug regimen.

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Abbreviations

BPD	bronchopulmonary dysplasia
ELBW	extremely low birth weight
MRI	magnetic resonance imaging

REFERENCES

1. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001; 163:1723–1729. [PubMed: 11401896]
2. Schmidt B, Asztalos EV, Roberts RS, Sauve RS, Whitfield MF. Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA*. 2003; 289:1124–1129. [PubMed: 12622582]
3. Halliday HL, Ehrenkranz RA, Doyle LW. Early (<8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2010;CD001146. [PubMed: 20091516]
4. Wilson-Costello D, Walsh MC, Langer JC, Guillet R, Laptook AR, Stoll BJ, et al. Impact of postnatal corticosteroid use on neurodevelopment at 18 to 22 months' adjusted age: effects of dose,

- timing, and risk of bronchopulmonary dysplasia in extremely low birth weight infants. *Pediatrics*. 2009; 123:e430–e437. [PubMed: 19204058]
5. Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC. Impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk for chronic lung disease. *Pediatrics*. 2005; 115:655–661. [PubMed: 15741368]
 6. Parikh NA, Lasky RE, Kennedy KA, Moya FR, Hochhauser L, Romo S, et al. Postnatal dexamethasone therapy and cerebral tissue volumes in extremely low birth weight infants. *Pediatrics*. 2007; 119:265–272. [PubMed: 17272615]
 7. Thompson DK, Wood SJ, Doyle LW, Warfield SK, Lodygensky GA, Anderson PJ, et al. Neonate hippocampal volumes: prematurity, perinatal predictors, and 2-year outcome. *Ann Neurol*. 2008; 63:642–651. [PubMed: 18384167]
 8. Sloviter RS, Sollas AL, Neubort S. Hippocampal dentate granule cell degeneration after adrenalectomy in the rat is not reversed by dexamethasone. *Brain Res*. 1995; 682:227–230. [PubMed: 7552318]
 9. Huang CC, Lin HR, Liang YC, Hsu KS. Effects of neonatal corticosteroid treatment on hippocampal synaptic function. *Pediatr Res*. 2007; 62:267–270. [PubMed: 17622955]
 10. Doyle LW, Ehrenkranz RA, Halliday HL. Postnatal hydrocortisone for preventing or treating bronchopulmonary dysplasia in preterm infants: a systematic review. *Neonatology*. 2010; 98:111–117. [PubMed: 20150750]
 11. Watterberg KL. American Academy of Pediatrics. Committee on Fetus and Newborn. Policy statement--postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. *Pediatrics*. 2010; 126:800–808. [PubMed: 20819899]
 12. Papile LA, Tyson JE, Stoll BJ, Wright LL, Donovan EF, Bauer CR, et al. A multicenter trial of two dexamethasone regimens in ventilator-dependent premature infants. *N Engl J Med*. 1998; 338:1112–1118. [PubMed: 9545359]
 13. Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB. the DART Study Investigators. Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: a multicenter, international, randomized, controlled trial. *Pediatrics*. 2006; 117:75–83. [PubMed: 16396863]
 14. Yu X, Zhang Y, Lasky RE, Datta S, Parikh NA, Narayana PA. Comprehensive brain MRI segmentation in high risk preterm newborns. *PLoS One*. 2010; 5:e13874. [PubMed: 21079730]
 15. Hüppi PS, Warfield S, Kikinis R, Barnes PD, Zientara GR, Jolesz FA, et al. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. *Ann Neurol*. 1998; 43:224–235. [PubMed: 9485064]
 16. Watterberg KL, Gerdes JS, Gifford KL, Lim KM. Prophylaxis against early adrenal insufficiency to prevent chronic lung disease in premature infants. *Pediatrics*. 1999; 104:1258–1263. [PubMed: 10585975]
 17. Watterberg KL, Gerdes JS, Cole CH, Aucott SW, Thilo EH, Mammel MC, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. *Pediatrics*. 2004; 114:1649–1657. [PubMed: 15574629]
 18. Peltoniemi O, Kari MA, Heinonen K, Saarela T, Nikolajev K, Andersson S, et al. Pretreatment cortisol values may predict responses to hydrocortisone administration for the prevention of bronchopulmonary dysplasia in high-risk infants. *J Pediatr*. 2005; 146:632–637. [PubMed: 15870666]
 19. Bonsante F, Latorre G, Iacobelli S, Forziati V, Laforgia N, Esposito L, et al. Early low-dose hydrocortisone in very preterm infants: a randomized, placebo-controlled trial. *Neonatology*. 2007; 91:217–221. [PubMed: 17568152]
 20. van der Heide-Jalving M, Kamphuis PJ, van der Lann MJ, Bakker JM, Wiegant VM, Heijnen CJ, et al. Short- and long-term effects of neonatal glucocorticoid therapy: is hydrocortisone an alternative to dexamethasone? *Acta Paediatr*. 2003; 92:827–835. [PubMed: 12892163]
 21. Biswas S, Buffery J, Enoch H, Bland M, Markiewicz M, Walters D. Pulmonary effects of triiodothyronine (T3) and hydrocortisone (HC) supplementation in preterm infants less than 30 weeks gestation: results of the THORN trial—thyroid hormone replacement in neonates. *Pediatr Res*. 2003; 53:48–56. [PubMed: 12508081]

22. Lodygensky GA, Rademaker K, Zimine S, Gex-Fabry M, Liefink AF, Lazeyras F, et al. Structural and functional brain development after hydrocortisone treatment for neonatal chronic lung disease. *Pediatrics*. 2005; 116:1–7. [PubMed: 15995023]
23. Karemaker R, Heijnen CJ, Veen S, Baerts W, Samsom J, Visser GH, et al. Differences in behavioral outcome and motor development at school age after neonatal treatment for chronic lung disease with dexamethasone versus hydrocortisone. *Pediatr Res*. 2006; 60:745–750. [PubMed: 17065571]
24. Rademaker KJ, Uiterwaal CS, Groenendaal F, Venema MM, van Bel F, Beek FJ, et al. Neonatal hydrocortisone treatment: neurodevelopmental outcome and MRI at school age in preterm-born children. *J Pediatr*. 2007; 150:351–357. [PubMed: 17382109]
25. Benders MJ, Groenendaal F, van Bel F, Ha Vinh R, Dubois J, Lazeyras F, et al. Brain development of the preterm neonate after neonatal hydrocortisone treatment for chronic lung disease. *Pediatr Res*. 2009; 66:555–559. [PubMed: 19851225]
26. Tam EW, Chau V, Ferriero DM, Barkovich AJ, Poskitt KJ, Studholme C, et al. Preterm cerebellar growth impairment after postnatal exposure to glucocorticoids. *Sci Transl Med*. 2011; 3:105ra105.
27. Watterberg KL, Shaffer ML, Mishefske MJ, Leach CL, Mammel MC, Couser RJ, et al. Growth and neurodevelopmental outcomes after early low-dose hydrocortisone treatment in extremely low birth weight infants. *Pediatrics*. 2007; 120:40–48. [PubMed: 17606560]
28. Peltoniemi OM, Lano A, Puosi R, Yliherva A, Bonsante F, Kari MA, et al. Neonatal Hydrocortisone Working Group. Trial of early neonatal hydrocortisone: two-year follow-up. *Neonatology*. 2009; 95:240–247. [PubMed: 18931525]
29. Stark AR, Carlo WA, Tyson JE, Papile LA, Wright LL, Shankaran S, et al. Adverse effects of early dexamethasone in extremely-low-birth-weight infants. *N Engl J Med*. 2001; 344:95–101. [PubMed: 11150359]
30. Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB. DART Study Investigators. Outcome at 2 years of age of infants from the DART study: a multicenter, international, randomized, controlled trial of low-dose dexamethasone. *Pediatrics*. 2007; 119:716–721. [PubMed: 17403842]
31. Yoder BA, Harrison M, Clark RH. Time-related changes in steroid use and bronchopulmonary dysplasia in preterm infants in very preterm infants. *Pediatrics*. 2009; 124:673–679. [PubMed: 19620192]
32. Woodward LJ, Edgin JO, Thompson D, Inder TE. Object working memory deficits predicted by early brain injury and development in the preterm infant. *Brain*. 2005; 128:2578–2587. [PubMed: 16150850]

Figure 1.
Flow diagram of the patient progress through the parallel randomized trial of two groups.

Table I

Baseline Demographic and Clinical Characteristics of the Infants at Randomization and their Mothers.

Characteristics Mothers	Hydrocortisone Group (N = 31)	Placebo Group (N = 33)
Age, median (IQR), yr	24 (20 – 30)	26 (22 – 31)
Race, non-Caucasian, n (%)	14 (45%)	15 (45%)
Antenatal steroids, n (%)	25 (81%)	20 (61%)
Maternal hypertension, n (%)	11 (35%)	10 (30%)
Infants at birth		
Gestational age, median (IQR) wk	25 (24 – 26)	25 (24 – 27)
Birth weight, g, mean (SD)	677 (107)	655 (142)
Male sex, n (%)	14 (45%)	20 (61%)
Small for gestational age (<10 th), n (%)	6 (19%)	10 (30%)
Multiple births, n (%)	6 (19%)	9 (27%)
Apgar at 5 min, median (IQR)	7 (5 – 8)	7 (5 – 8)
Outborn, n (%)	7 (23%)	7 (21%)
Infants at randomization		
Age, median (IQR), d	17 (14 – 19)	16 (13 – 20)
Surfactant use, n (%)	31 (100%)	32 (97%)
Mean airway pressure, cm H ₂ O	9.9 (8.1 – 11.0)	9.0 (7.8 – 10.4)
Fraction of inspired oxygen, median (IQR)	0.44 (0.38 – 0.60)	0.46 (0.36 – 0.52)
Respiratory index score, median (IQR)	4.3 (3.0 – 6.1)	4.0 (3.4 – 5.4)

Table II

Total and Regional Brain Volume Outcomes before the First Discharge Home. *

Total and Regional Brain Volume Outcomes (in cm ³)	Hydrocortisone Group (N=23)	Placebo Group (N=21)	Group Difference in Unadjusted Means	Difference in Means Adjusted for PMA at MRI (95% CI)	P Value	Difference in Means Adjusted for PMA at MRI and Patient Characteristics [†] (95% CI)	P Value
Total brain tissue	272.01 ±40.30	277.82 ±59.05	-5.81 (-36.33, 24.71)	6.35 (-20.82, 32.54)	0.64	5.40 (-19.49, 30.29)	0.66
Cerebral white matter [@]	122.45 ±18.73	118.62 ±17.51	3.83 (-7.62, 15.29)	6.06 (-4.42, 16.55)	0.25	6.35 (-3.27, 15.96)	0.19
Cortical gray matter [@]	105.58 ±18.16	115.58 ±37.86	-10.00 (-28.35, 8.35)	-4.85 (-20.23, 10.52)	0.53	-3.57 (-18.30, 11.15)	0.63
Cerebrospinal fluid	81.23 ±25.77	86.96 ±31.53	-5.74 (-23.19, 11.72)	1.37 (-13.56, 16.32)	0.85	1.33 (-12.97, 15.62)	0.85
Cerebellum	15.91 ± 4.58	17.98 ±5.59	-2.06 (-5.16, 1.04)	-0.32 (-2.45, 1.82)	0.77	-0.18 (-2.27, 1.90)	0.86
Hippocampi [@]	1.29 ± 0.23	1.35 ±0.27	-0.06 (-0.22, 0.10)	-0.05 (-0.21, 0.11)	0.51	-0.05 (-0.21, 0.11)	0.53
Subcortical gray matter [@]	18.16 ±2.22	17.90 ±3.17	0.27 (-1.44, 1.98)	0.59 (-0.98, 2.16)	0.45	0.60 (-0.93, 2.13)	0.43
Thalamus [@]	7.69 ±1.04	7.60 ±1.45	0.09 (-0.72, 0.90)	0.27 (-0.45, 0.99)	0.46	0.26 (-0.45, 0.96)	0.46
Lenticular nuclei [@]	5.37 ±0.81	5.21 ±1.05	0.16 (-0.43, 0.75)	0.22 (-0.37, 0.80)	0.45	0.22 (-0.34, 0.78)	0.44
Caudate [@]	2.82 ±0.54	2.73 ±0.62	0.09 (-0.28, 0.45)	0.16 (-0.17, 0.49)	0.34	0.19 (-0.14, 0.52)	0.25
Accumbens nuclei [@]	0.45 ±0.12	0.45 ±0.15	0.00 (-0.09, 0.08)	-0.01 (-0.10, 0.07)	0.77	-0.02 (-0.09, 0.06)	0.69
Corpus Callosum [@]	0.96 ±0.22	0.91 ±0.26	0.05 (-0.10, 0.20)	0.04 (-0.11, 0.19)	0.59	0.02 (-0.13, 0.16)	0.83
Amygdalae [@]	0.55 ±0.15	0.55 ±0.16	0.00 (-0.1, 0.09)	0.01 (-0.08, 0.10)	0.82	0.00 (-0.09, 0.09)	0.97
Brain stem [@]	5.59 ±0.64	5.97 ±1.07	-0.38 (-0.92, 0.17)	-0.22 (-0.69, 0.26)	0.36	-0.15 (-0.61, 0.32)	0.52

* Plus-minus values are means ± SD.

[@] This outcome determined for 22 hydrocortisone and 19 placebo treated surviving infants.[†] Patient characteristics included respiratory index score, sex, and antenatal steroids.

CI denotes confidence interval; PMA denotes postmenstrual age.

Table III

Mortality and Respiratory Outcomes Before or at 36 Weeks Postmenstrual Age.

Outcome	Hydrocortisone Group (N=31)	Placebo Group (N=33)	Risk Ratio with Hydrocortisone (95% CI)	Difference in Means (95% CI)	P Value
Survival without severe BPD	3/31 (10%)	5/32 (16%)	0.62 (0.13, 2.66)		0.49
Death	8/31 (26%)	8/33 (24%)	1.06 (0.46, 2.48)		0.89
Days on positive pressure support [§]	68.7 (63.4–74.0)	65.9 (59.7–72.0)		2.8 (–10.7, 5.1)	0.47
Adjusted mean [†]				3.1 (–4.9, 11.2)	0.43
Days on supplemental oxygen [§]	72.7 (68.0–77.4)	72.0 (66.9–77.1)		0.7 (–7.5, 6.0)	0.83
Adjusted mean [†]				1.0 (–5.9, 8.0)	0.76

[§]Mean (95% CI); reported for survivors only.[†]Adjusted for respiratory index score, sex, and antenatal steroids.

CI denotes confidence interval.

Table IV

Anthropometry at 36 weeks Postmenstrual Age and Rates of Complications After Randomization.*

	Placebo Group (N = 33)	Hydrocortisone (N = 31)	P Value
Anthropometry at 36 weeks *			
Head circumference, cm	29±2	29±2	0.74
Weight, g	1775 ± 319	1781±366	0.95
Length, cm	41±3	41±3	0.83
Acute Adverse Events			
Spontaneous intestinal perforation, n (%)	0 (0%)	2 (6%)	0.23
Necrotizing enterocolitis, n (%)	3 (9%)	4 (13%)	0.70
Late-onset bacteremia/sepsis, n (%)	15 (45%)	13 (42%)	0.81
Glucose >130 mg/dL, n (%)	13 (39%)	16 (52%)	0.45
Systolic BP >90 mm Hg, n (%)	13 (39%)	17 (55%)	0.21

* Plus minus values are means ± SD from 23 survivors for each group