Hydrocortisone Treatment for Bronchopulmonary Dysplasia and Brain Volumes in Preterm Infants

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Objective To assess whether there was an adverse effect on brain growth after hydrocortisone (HC) treatment for bronchopulmonary dysplasia (BPD) in a large cohort of infants without dexamethasone exposure.

Study design Infants who received HC for BPD between 2005 and 2011 and underwent magnetic resonance imaging at term-equivalent age were included. Control infants born in Geneva (2005-2006) and Utrecht (2007-2011) were matched to the infants treated with HC according to segmentation method, sex, and gestational age. Infants with overt parenchymal pathology were excluded. Multivariable analysis was used to determine if there was a difference in brain volumes between the 2 groups.

Results Seventy-three infants treated with HC and 73 matched controls were included. Mean gestational age was 26.7 weeks, and mean birth weight was 906 g. After correction for gestational age, postmenstrual age at time of scanning, the presence of intraventricular hemorrhage, and birth weight *z*-score, no differences were found between infants treated with HC and controls in total brain tissue or cerebellar volumes.

Conclusions In the absence of associated parenchymal brain injury, no reduction in brain tissue or cerebellar volumes could be found at term-equivalent age between infants with or without treatment with HC for BPD. *(J Pediatr 2013;163:666-71)*.

Bronchopulmonary dysplasia (BPD) remains a common complication of extremely preterm birth. Risk factors for the development of BPD, such as difficulty in weaning an infant from the ventilator or prolonged oxygen requirement in the first weeks of life, are even more frequently encountered. Treatment options are limited. If conservative care with less aggressive ventilator settings, treatment of a hemodynamic significant patent ductus arteriosus, fluid restriction, and/or diuretics is not sufficient, a decision can be made to treat with corticosteroids, with dexamethasone used most commonly. Although the short-term effects of dexamethasone prescription on pulmonary function are satisfactory, effects on long-term neurodevelopmental outcome are not.[1] Preterm infants treated with dexamethasone had a higher rate of cerebral palsy and cognitive impairment and more often needed special education at early school age.[2-4] The origin of these adverse sequelae may be represented by as smaller brain volumes at term-equivalent age.[5,6] Therefore, treatment with dexamethasone is not recommended and should be restricted to the most severe cases.

Hydrocortisone (HC) is an alternative treatment option. Although somewhat less potent, if given moderately early (between 5-25 days after birth), the effects on pulmonary function are similar. There is not much research on long-term outcomes after the use of HC, but several studies have not shown any difference between HC-treated infants and controls regarding rates of cerebral palsy and other neuromotor deficits and cognitive development.[7-10] Two studies have reported on the effect of HC on brain volumes at term-equivalent age. Benders et al described a small cohort of preterm infants without associated brain injury and did not find any differences between HC-treated infants and controls.[11] However, Tam et al described a larger cohort and found a difference in cerebellar size at term-equivalent age after treatment with HC.[12] Important drawbacks of the study by Tam et al were that part of these infants also received dexamethasone and infants with parenchymal brain lesions were included.

Our aim was to assess whether there was an adverse effect on brain volume at term-equivalent age after HC treatment for BPD in a cohort of preterm infants without dexamethasone exposure.

3D	3-Dimensional
BPD	Bronchopulmonary dysplasia
HC	Hydrocortisone
IVH	Intraventricular hemorrhage
MR	Magnetic resonance
MRI	Magnetic resonance imaging
TE	Echo time
TR	Repetition time

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Methods

A combined cohort was formed containing children from Geneva and Utrecht. Infants from Utrecht, who received HC for BPD between 2005 and 2011 and had magnetic resonance imaging (MRI) at term-equivalent age, were included. Infants born between 2005-2006 have been described previously.[11] For those previously described infants, parental informed consent was given. For the other infants, clinically indicated magnetic resonance (MR) images were used with permission from the ethical review board of our institution. HC was given starting at a postnatal age of ≥7 days, in ventilator-dependent infants with need for supplemental oxygen, if this could not be accounted for by an infection or a patent ductus arteriosus. Standard clinical dosage schemes were followed, starting with a dosage of 5 mg/kg/d divided in 4 doses for 1 week and a subsequent tapering course every 5 days, leading to a total treatment duration of 22 days and a standard cumulative dosage of 72.5 mg/kg. This scheme could be adjusted at the discretion of the attending neonatologist. Infants treated with HC were matched to control infants born in both Geneva (2005-2006) and Utrecht (2007-2011). Control infants were matched for sex and gestational age. Matching was performed in subgroups, taking into account that infants were matched with controls scanned with the same imaging protocol and segmented with the same automatic method. Clinical variables were extracted from patient charts. Cerebral lesions were diagnosed on the basis of serial cranial ultrasound and MRI results. The presence of an intraventricular hemorrhage (IVH), graded according to Papile et al,[13] white matter damage, and large cerebellar hemorrhages was recorded. Infants with a large parenchymal hemorrhage (1 infant) or a large cerebellar hemorrhage (1 infant) were excluded. In all infants with posthemorrhagic ventricular dilatation, a stable situation with a decrease in ventricular size was reached soon after the initiation of treatment. Three infants in the HC-treated group had a reservoir inserted but none required a permanent shunt. There were no infants with evidence of cystic periventricular leukomalacia on their cranial ultrasound and MRI examinations.

MRI Examination

MRI was performed around term-equivalent age in all infants. Infants born in 2005 and 2006 were scanned with use of a 1.5-T MR system (Philips Medical Systems, Best, The Netherlands). The protocol included a 3-dimensional (3D) T1 fast-gradient echo sequence (repetition time [TR] 15 ms, echo time [TE] 4.4 ms, slice thickness 1.5 mm) and a T2 fast-spin echo sequence (TR 3500 ms, TE 30/150 ms, slice thickness 1.5 mm), both in the coronal plane.

Infants born in 2007 or later were scanned with use of a 3.0-T MR system (Achieva; Philips Medical Systems) using the sense head coil. Between 2007 and June 2008, the imaging protocol contained axial 3D T1-weighted and T2-weighted images (TR 9.4 ms, TE 4.6 ms, and slice thickness 2.0 mm; and TR 6293 ms, TE 120 ms, and slice thickness 2.0 mm, respectively). From June 2008 on, 3D T1-weighted and T2-weighted images were acquired in the coronal plane (3D T1-weighted: TR 9.5 ms, TE 4.6 ms, and slice thickness 1.2 mm; 3D T2-weighted: TR 4847 ms, TE 150 ms, and slice thickness 1.2 mm).

Infants were sedated using oral chloral hydrate 50-60 mg/kg. Heart rate, transcutaneous oxygen saturation, and respiratory rate were monitored. Minimuffs (Natus Medical Inc, San Carlos, California) were used for hearing protection. All MR examinations were reevaluated by 2 experienced neonatologists. Lesions seen on conventional imaging were scored. Infants with evident tissue loss on MRI (eg, porencephaly due to a periventricular hemorrhagic infarction or a large cerebellar lesion destroying more than one-half of the cerebellar hemisphere) were excluded (2 patients, as described earlier).

Volumetric Measurements

Brain tissue and cerebellum were segmented automatically. Considering that infants were scanned using 2 different imaging protocols on scanners of a different field strength, we chose to use the segmentation method best fitted for the acquisition of the data per imaging protocol. Therefore, segmentations were performed using 2 different segmentation methods. For the children born before 2007 in both Utrecht and Geneva, tissues were segmented using the method described by Warfield et al.[14] The method segments cortical gray matter, deep gray matter, unmyelinated white matter, myelinated white matter, and cerebrospinal fluid, but it does not allow separate delineation of the cerebellum. Therefore, cerebellar tissue was manually outlined in T2-weighted scans and volumes were corrected accordingly. Details from this method have been described previously.[11] For the infants born in 2007 or later, the algorithm of the method of Anbeek et al was adjusted to segment 3T scans.[15,16] In addition to the mentioned tissues, this algorithm delineates cerebellum, basal ganglia, brainstem, and separation of the cerebrospinal fluid in the ventricles from cerebrospinal fluid outside the brain. Cerebellar segmentations in this group were thus automatically generated. Total brain tissue volume and intracranial volume were calculated from the segmentations. The Anbeek et al[15,16] method was developed for axially acquired images. However, we tested for a difference in volumes between coronal and axial acquired images in a subgroup of 5 infants and did not find any differences in volumes (paired *t* tests: cerebellum, $P = .245$; total brain volume, $P = .783$). In addition, to confirm the quality of the automatically obtained segmentations, results were visually inspected. This allowed us to combine these sets into 1 cohort.

Statistical Analyses

Statistical procedures were performed using both IBM SPSS Statistics version 20 (SPSS Inc, Chicago, Illinois) and R version 2.15.0 (www.r-project.org/).[17] Baseline characteristics between the 2 groups were compared using independent-sample *t* tests. For multivariable analysis, general linear modeling was used with brain volume as dependent variable. A

cutoff value of $P = .05$ was used. All patients with HC were included, and a matched sample of all other patients without HC use and with available MRI. Brain volumes were analyzed with individual patients in the regression model. Earlier studies reported a decrease in brain volume of 20% for cerebellar volume and 10%-30% for total cerebral tissue volume after the use of dexamethasone.[5,6] Sample size calculations were performed, taking into account the ability to show the presence or absence of an effect one-half the size of dexamethasone, so a 10% difference in brain volumes. Sample size calculations demonstrated that this difference of 10% in brain volumes could be demonstrated with an α of 0.05, a power of 0.9, and a sample size of 55 patients in each arm.

Because postmenstrual age at the time of scanning, gestational age, and birth weight influence total brain volumes, we included these variables in our model.[18-20] We also included the presence of an IVH. Separate analysis of infants with mild posthemorrhagic ventricular dilatation, minor punctate white matter lesions, or punctate cerebellar hemorrhages revealed no significant differences in volumes. Therefore, these patients were included in the final analysis. Corticosteroid use was analyzed in 2 ways: binomial (yes/no) and as total cumulative dosage per kilogram up to the day of MRI. Because distribution of HC was skewed, we used the natural logarithm of this variable. Also, to screen whether a high dose of HC would have an effect where a low dose did not, we repeated the analysis with HC divided as none, a cumulative dosage <50 mg/kg, and a cumulative dosage >50 mg/kg. Interaction of gestational age and HC was tested in the model. Postmenstrual age at time of scanning was calculated as the difference from 40.0 weeks' postmenstrual age and gestational age as the difference from 24.0 weeks' (our youngest included infants were born at that gestation). Birth weights are represented using a z score. All statistical analyses were also performed within each subgroup (eg, infants segmented with the Warfield et al[14] method and with the Anbeek et al[15,16] method) to further quantify any possible differences between groups.

Results

A total of 75 infants treated with HC and 75 control infants were included. Two infants treated with HC had evident tissue loss on their MRI (1 porencephaly and 1 large cerebellar hemorrhage) and thus were excluded. The remaining 73 infants with HC treatment and 73 control infants were eligible for analysis. Despite matching, infants treated with HC had a significantly lower birth weight ($P = .01$, Table I). Weight at scan, however, did not differ significantly ($P = .25$). Concurrent with the more severe pulmonary problems, the grade of respiratory distress syndrome[21] and days of mechanical ventilation were significantly higher in infants treated with HC compared with controls ($P = .00$ and $P = .05$, respectively). Because HC was given as part of clinical practice at the discretion of the attending neonatologist, not all infants received the same cumulative dosage. In some children, HC was tapered sooner because of significant improvement or side effects such as hypertension. In other infants, a longer treatment or a slower tapering course was given because of a relapse after the first tapering steps. This led to a wide range in the cumulative dosage of HC, between

Table I. Clinical variables

Variable	Infants treated with HC (n = 73)	Control infants (n = 73)	*P* value
Gestational age, wk (SD, range)	26.6 (1.35, 24.3-30.4)	26.9 (1.34, 24.3-30.4)	.12
Sex, No. male/female	40/33	36/37	.51
Birth weight, g (SD)	863 (205)	948 (166)	.01
Birth weight *z* score	0.06	0.40	.02
Antenatal steroids, %	70	77	.70
Mechanical ventilation, median d (25th-75th percentile)	16 (12-21)	4 (0-7)	.05
Grade RDS, No.			.00
None	4	21	
Grade 1	2	3	
Grade 2	15	31	
Grade 3	28	11	
Grade 4	24	7	
Postmenstrual age at time of scanning, wk (SD)	41.1 (0.76)	41.1 (0.75)	.67
Weight at time of scanning, g (SD)	3182 (571)	3280 (459)	.25
Presence of IVH, No.			.001
None	41	60	
Grade 1-2	24	12	
Grade 3	7	1	
Grade 4	0	0	
Cerebellar hemorrhage, No.			.79
None	69	68	
<6 Punctate lesions	3	4	
>6 Punctate lesions	1	1	
Posthemorrhagic ventricular dilatation requiring intervention, No.			.05
Lumbar punctures	3	1	
Placement of a reservoir	3	0	

RDS, respiratory distress syndrome.

Table III. Multivariable analysis

Model/factor	Coefficient, mL	95% CI	*P* value
Total brain tissue volume: final model			
Postmenstrual age at scan, wk	18.2	9.2 to 27.3	.00
Birth weight *z* score	11.2	3.3 to 19.2	.00
Gestational age, wk	6.8	1.7 to 12.0	.01
HC, yes/no	−12.5	−26.3 to 1.4	.08
Cerebellar volume: final model			
Postmenstrual age at scan, wk	2.1	1.3 to 2.9	.00
Birth weight *z* score	2.2	1.6 to 2.9	.00
Grade 3 IVH	−2.2	−4.4 to 0.1	.06
HC, yes/no	−0.53	−1.8 to 0.7	.39

In the model, postmenstrual age is taken as the difference from 40 wk, and gestational age as the difference from 24 wk. IVH is graded according to Papile et al.[13]

16 and 216 mg/kg with a mean of 77 mg/kg. Also, although children with evidence of tissue loss were excluded, the presence of an IVH did show a significant difference ($P = .00$, Table I). The presence of an IVH may have an adverse effect on cerebellar volumes.[22] Therefore, the presence of a grade 3 IVH was included as a factor in the multivariable analysis. There were no infants with evidence of cystic periventricular leukomalacia on their cranial ultrasound and MRI in this cohort.

Uncorrected brain volumes are shown in Table II (available at www.jpeds.com). The results of the multivariable analysis are shown in Table III. There was no significant difference in total brain tissue volume between HC-treated and control infants ($P = .08$). Only postmenstrual age at MRI, birth weight *z* score, and gestational age at birth were significant factors in the multivariable model. Repeating the analysis using the cumulative dosage of HC gave the same results ($P = .1$), as did the analysis with HC divided into high and low dosages ($P = .11$ and $P = .28$, respectively).

We also performed these analyses for cerebellar volumes, because previous literature suggested that this brain structure may especially be affected by the use of HC.[12] Multivariable analysis showed postmenstrual age at time of scan, birth weight *z* score, and grade 3 IVH to be of significant influence on cerebellar volumes at term-equivalent age. Again, neither HC as a binomial factor ($P = .39$) nor the cumulative dosage of HC ($P = .07$), or the divided dosages ($P = .26$ for the high and $P = .82$ for the low dosage), were significant. Although infants with large cerebellar hemorrhages were excluded, we did include infants with punctate lesions in the cerebellum. When repeating the analysis after exclusion of these children, the resulting models were the same. Therefore, these children remained included in the analysis.

The results of the subgroup analysis were identical to those of the entire cohort and are therefore not represented separately.

Discussion

In this cohort of 146 preterm infants, HC treatment for BPD was not associated with a reduction in total brain tissue volume or cerebellar volume. Only postmenstrual age at time of scanning, gestational age, and birth weight *z* score had a significant effect on total brain tissue volume. Postmenstrual age at time of scanning, birth weight *z* score, and the presence of a grade 3 IVH had a significant effect on the cerebellar volumes at term-equivalent age. These are all known factors to adversely affect brain volumes.[18-20,22]

The lack of effect of HC on brain volumes is consistent with previous reports from our group describing short- and long-term effects of HC. Benders et al described a small subset of this cohort and were unable to find any differences in brain volumes.[11] This absence of volumetric differences seems to persist into childhood. Lodygensky et al showed in a cohort of 60 preterm children that brain volumes and neurocognitive outcome at 8 years did not differ between children treated with HC and preterm controls.[23] The lack of effect of HC on long-term neurodevelopmental outcome has also been shown in several follow-up studies.[7-10,24] In contrast, Tam et al showed that in their cohort of 172 infants, cerebellar volume was negatively affected by the use of both dexamethasone and HC.[12] However, only 31 subjects received postnatal HC and 11 of those received both HC and dexamethasone. Also, infants with large cerebellar hemorrhages were included in the analysis, although multivariable correction was used. Tam et al found a negative effect of 8% on cerebellar volumes after the use of HC.[12] Allin et al previously reported an 8% decrease of cerebellar volume in preterm infants compared with healthy term controls at 15 years of age. This decrease had a negative correlation with long-term cognitive outcome.[25] An 8% difference, therefore, seems to have clinical relevance. An additional power calculation demonstrated that in our 146 patients, the power to detect a difference of 8% in brain volumes with an α of 0.05 would be 0.85. In addition, based on the observations of dexamethasone, the potential effect of HC is to diminish and not to increase brain volumes, a 1-sided test could be used. In this case, the power of our study of 146 infants divided over 2 groups of 73 would be 0.92, which is high.

Previous studies on volumetric changes after dexamethasone use have shown decreases in cerebellar volume of 20% and in total cerebral tissue volume of 10%-30%.[5,6] The effect sizes found in this study are, besides not being significant, very small. The effect size of HC on cerebellar volume is −0.5 mL. With a mean cerebellar volume of 28.4 mL in the control infants, this would mean a decrease of 1.8%. For total brain volume, the same calculation would lead to a decrease of 3.3% (mean volume 378.2 mL, effect size −12.5 mL). These values are much smaller than those presented by Tam et al,[12] and this difference may be partially explained by the concomitant use of dexamethasone and HC in part of their cohort.

Dexamethasone has long been known to have a detrimental effect on brain growth and maturation in the preterm infant and has been extensively studied in animal experiments.[26,27] There are several hypotheses on why there is such a difference in adverse long-term effects between dexamethasone and HC. First, dexamethasone mainly interacts with the glucocorticoid receptor of the brain, whereas HC primarily uses

the mineralocorticoid receptors.[28] Activation of the glucocorticoid receptor leads to adverse neuronal effects.[29] Second, during gestation, the enzyme 11β-hydroxysteroiddehydrogenase-2 is widely expressed in the fetal or preterm brain. This enzyme will metabolize the active HC to the inactive 11-dehydro form, thus lowering the active dosage and protecting the developing brain from excessive corticosteroid exposure.[30,31] Dexamethasone is a synthetic glucocorticoid, and there is no equivalent enzyme for dexamethasone in the human brain. Third, the effective dosage of HC given is often lower than the comparable dosage dexamethasone, resulting in a lower cumulative dosage that can cause toxic effects.[32,33] Our standard dose scheme of a total 72.5 mg/kg HC is substantially higher than in most other studies reporting on HC use, where total doses between 6 and 30 mg/kg were given.[33] However, the equivalent dosage of dexamethasone in our patients would be approximately 2-3 mg/kg. Most trials reporting on dexamethasone used higher dosage schemes.[32] Another possible cause for a difference in accumulation is the shorter biological half-life of HC (8-12 hours) compared with dexamethasone (36-72 hours).[34] Again, this could explain a difference in toxic effects.

There are several limitations to our study. First, the study was retrospective, limiting our ability to detect confounders. Second, 2 different acquisition protocols were used; however, infants were matched within protocol. Third, we excluded infants with cystic parenchymal brain lesions, which may have selected healthier infants but did avoid the possible effect of large white matter lesions on cerebellar volumes.[22,35] Fourth, we cannot comment on the underlying microstructure of the brain, which may be altered by HC exposure. And last, this was a short-term, structural study; we did not evaluate the relationship of brain volume to neurodevelopmental outcomes.

In conclusion, we could not demonstrate any differences in brain volumes between children treated with HC for BPD and nontreated controls at term-equivalent age in this cohort. Combined with the earlier reported lack of effect on long-term developmental outcome, HC seems to be a safer alternative than dexamethasone in the treatment of BPD. ■

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50 Years Ago in *The Journal of Pediatrics*

Children of Mothers with Phenylketonuria

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The observation of mental retardation in 5 offspring of a woman with a diagnosis of poorly-controlled phenylketonuria (PKU) was the first report of the hypothesis that abnormal phenylalanine metabolism during pregnancy could lead to development disabilities in offspring who are not affected by PKU. The condition in infants born to women with poorly controlled PKU was given the confusing term maternal PKU, even though it applies to the infant. Subsequent studies have clearly shown the relationship between persistently elevated plasma phenylalanine in mothers and the congenital anomalies and developmental disabilities that result in the offspring. With the success of newborn screening and the dietary management of PKU, many women with PKU have had healthy offspring if they are rigorous in their phenylalanine control at the time of conception and throughout their pregnancy. Because compliance with PKU treatment falls off significantly as patients enter their teenage years, a major effort to counsel females about their risk for abnormal infants is necessary. Young adult females with PKU who are in poor metabolic control should be offered referral to a metabolic genetic clinic and contraception until they have achieved good control. New oral pharmaceuticals and injectable enzymes replacement therapies for patients with PKU, which have been approved or are in late clinical trials, will offer previously unavailable therapeutic options to prevent the effects of maternal PKU.

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Table II. Brain volumes for the different tissue classes, per segmentation method, uncorrected for postmenstrual age at time of scanning, gestational age, or birth weight

	Warfield et al[14] method		Anbeek et al[15,16] method	
	HC (n = 19)	Control (n = 19)	HC (n = 54)	Control (n = 54)
Cortical gray matter, mL (SD)	172 (32)	183 (38)	153 (22)	158 (17)
Unmyelinated white matter, mL (SD)	177 (27)	194 (33)	145 (23)	150 (21)
Cerebellum, mL (SD)	23 (4)	24 (5)	28 (4)	30 (3)
Cerebrospinal fluid, mL (SD)	49 (18)	57 (27)	101 (18)	101 (14)
Total brain tissue volume, mL (SD)	377 (57)	403 (64)	355 (39)	369 (34)
Intracranial volume, mL (SD)	426 (64)	460 (73)	455 (52)	471 (44)