Hydrocortisone Treatment for Bronchopulmonary Dysplasia and Brain Volumes in Preterm Infants

Karina J. Kersbergen, MD[1], Linda S. de Vries, MD, PhD[1], Britt J. M. van Kooij, MD, PhD[1], Ivana Išgum, PhD[2], Karin J. Rademaker, MD, PhD[1], Frank van Bel, MD, PhD[1], Petra S. Hüppi, MD[3], Jessica Dubois, PhD[3,4], Floris Groenendaal, MD, PhD[1], and Manon J. N. L. Benders, MD, PhD[1]

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

From the [1]Department of Neonatology, Wilhelmina Children's Hospital, [2]Image Sciences Institute, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Department of Pediatrics, Geneva University Hospitals, Geneva, Switzerland; and [4]Neurospin, Atomic Energy and Alternative Energies Commission, Paris, France

This study includes infants participating in the Neobrain study (LSHM-CT-2006-036534, contract number 036534), infants from an earlier study on preterm brain development funded by The Netherlands Organization for Health Research and Development (project 94527022), and infants from a study supported by the Royal Netherlands Academy of Arts and Sciences, the Termeulen fund, and the Young Investigator Exchange Program Fellowship of the International Pediatric Research Foundation. The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2013.04.001

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