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The Association of Dexamethasone and Hydrocortisone with Cerebellar Growth in Premature Infants

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Keywords
Cranial ultrasound · Corticosteroids · Chronic lung disease · Brain measurements · Extremely preterm infants

Abstract
Objectives: Corticosteroids are used to prevent or treat lung disease of prematurity. While neurological side effects have been reported, detailed effects on cerebellar growth are unknown. This study aimed to compare cerebellar growth in premature infants who received dexamethasone or hydrocortisone to premature infants who did not receive postnatal corticosteroids. ***Study Design:*** Retrospective case-control study in infants born at a gestational age of <29 weeks and admitted to two level 3 neonatal intensive care units. Exclusion criteria were severe congenital anomalies and cerebellar or severe supratentorial lesions. Infants were treated with dexamethasone (unit 1) or hydrocortisone (unit 2) for chronic lung disease. Controls (unit 1) did not receive postnatal corticosteroids. Sequential head circumference (HC) and ultrasound measurements of transcerebellar diameter (TCD), biparietal diameter (BPD), and corpus callosum-fastigium length (CCFL) were performed until 40 weeks' postmenstrual age (PMA). Growth was assessed using linear mixed models correcting for PMA at measurement, sex, HC z-score at birth, and a propensity score indicating illness severity. Group differences before treatment were assessed using linear regression. ***Results:*** 346 infants were included (68 dexamethasone, 37 hydrocortisone, 241 controls). Before starting corticosteroids, TCD, BPD, and HC measurements did not differ between patients and controls at a comparable PMA. After starting treatment, both types of corticosteroid had a negative association with TCD growth. BPD, CCFL, and HC growth were not negatively affected. ***Conclusion:*** Administration of dexamethasone and hydrocortisone are both associated with impaired cerebellar growth in premature infants without evident negative associations with cerebral growth.

Introduction

Chronic lung disease (CLD), also known as bronchopulmonary dysplasia, occurs in 10–25% of infants born prematurely at a gestational age (GA) of <32 weeks [1]. It is defined as need for respiratory support beyond 36

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weeks' postmenstrual age (PMA) [2]. Respiratory symptoms later in life are more common in CLD patients. In addition, these patients experience more rehospitalizations, have a higher need for respiratory medication, a reduced lung function, and a 2-fold increase in the risk of death from CLD after the age of 15 years [3, 4]. To prevent these long-term consequences, a multitude of treatment modalities including various (postnatal) corticosteroid regimens are applied [5]. However, corticosteroids have been associated with increased risk of cerebral palsy, reduced motor and cognitive skills, behavioral problems, and reduction of total brain volume [6–9].

The preterm brain and specifically the cerebellum is vulnerable to injury and suboptimal development during the preterm period [10, 11]. This is due to a rapid increase in size, volume [10], and maturation of the cerebellum during the third trimester of pregnancy [12], a high concentration of corticosteroid receptors [13], and an immature blood-brain barrier [14]. Data on the effect of corticosteroids on the developing cerebellum are, however, still limited.

Corticosteroids affect the development of the cerebellum on a cellular level by (prematurely) signaling the removal of the external granular layer, inducing apoptosis, inhibiting proliferation, and inducing differentiation in cerebellar granule cells [15–19]. These changes may impair cerebellar growth after corticosteroid treatment. Neuroimaging studies reporting on impaired cerebellar development included relatively small sample sizes or did not perform serial measurements [20–22].

Reduced cerebellar growth is associated with long-term impairment of motor skills and cognition, and behavioral and social deficits [23–26]. This, combined with evidence about the efficacy of corticosteroids for CLD, could be a reason to minimize the use of corticosteroids, choose a different type, dose, or route of administration, and carefully consider patient selection. Two recent trials showed that hydrocortisone in extremely premature infants did not result in increased neurodevelopmental impairment at 2 years of age, but one also showed that hydrocortisone did not significantly improve survival without moderate or severe CLD [27, 28]. This could be related to the varying effects among different corticosteroids; however, there have been no randomized controlled trials that compared the effects of dexamethasone and hydrocortisone directly [29].

The aim of this study was to compare cerebellar growth, by performing linear measurements on sequentially performed cranial ultrasound (cUS), in premature infants who received dexamethasone or hydrocortisone for CLD with cerebellar growth in premature infants who did not receive corticosteroid treatment. The hypothesis was, based on previous literature, that impairment of cerebellar growth would be related to corticosteroid administration and that this association would be stronger for dexamethasone than for hydrocortisone. Secondarily, this study aimed to investigate the associations of dexamethasone and hydrocortisone with cerebral growth.

Materials and Methods

In this retrospective case-control study, sequential cUS measurements of transcerebellar diameter (TCD) were obtained during admission to the neonatal intensive care unit (NICU) and compared between patients who did or did not receive dexamethasone or hydrocortisone treatment for prevention of CLD.

Patients

Patients were admitted to Departments of Neonatology at the Leiden University Medical Center (LUMC, unit 1) and the Isala Women and Children's Hospital in Zwolle (unit 2), both located in the Netherlands. Inclusion criteria were admission between January 2006 and December 2020 in unit 1 and between January 2009 and December 2020 in unit 2, GA at birth <29 weeks, length of admission >28 days, and ultrasound images of sufficient quality to reliably measure TCD on at least two different time points before 40 weeks' PMA. Infants who received both dexamethasone and hydrocortisone for CLD were excluded. For infants receiving corticosteroids, at least one measurement before and one after the onset of treatment were required before 40 weeks' PMA. Exclusion criteria were severe congenital abnormalities and severe perinatal brain injury (intraventricular hemorrhage with periventricular hemorrhagic infarction, post-hemorrhagic ventricular dilatation requiring intervention, cystic periventricular leukomalacia, grade 2 and 3 cerebellar hemorrhage according to the classification system by Boswinkel et al. [30]) diagnosed during NICU admission. Cases were treated with dexamethasone (unit 1) or hydrocortisone (unit 2) compliant with institutional practice and at the discretion of the medical team. Criteria for postnatal corticosteroid treatment included, in both units, the need for mechanical ventilation, with a high level of supplemental oxygen, and failed extubation, at least 7–14 days after birth. Control infants were all infants in unit 1 who met the aforementioned inclusion and exclusion criteria and did not receive postnatal corticosteroids. A standard course of dexamethasone consisted of a 2.30 mg/kg cumulative dose before and a 1.65 mg/kg cumulative dose after April 18, 2019 administered over 16 days. A standard course of hydrocortisone consisted of 72.5 mg/kg cumulative dose over 21 days.

Clinical Characteristics

Baseline characteristics were collected from patient files. Head circumference (HC) at birth consisted of the first measurement and was obtained within the first week. Z-scores for birth weight and HC were determined using PediTools Electronic Growth Chart Calculator Fenton 2013 preterm [31].

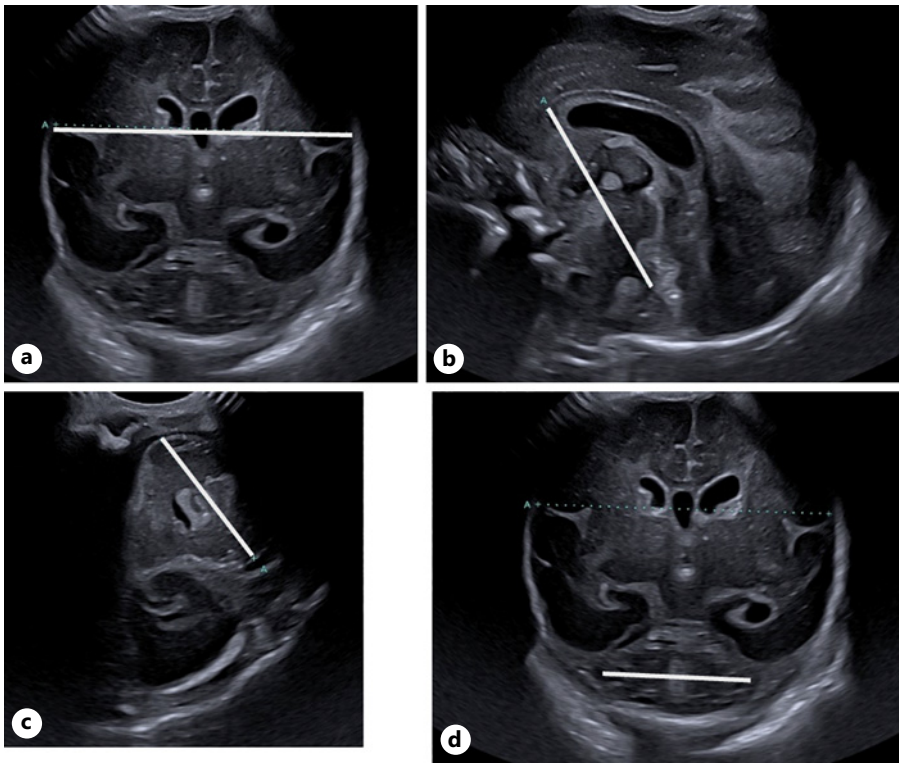

Fig. 1. Display of definitions for cUS measurements. **a** BPD. **b** CCFL. **c** TCD (mastoid fontanel). **d** TCD (anterior fontanel). BPD, biparietal diameter; CCFL, corpus callosum-fastigium length; TCD, transcerebellar diameter.

cUS Measurements

cUS examinations were performed by the attending neonatologist according to a standardized protocol for very preterm infants. In unit 1, cUS examination was performed with an Aloka Alpha 10 ultrasound system (Hitachi Medical Systems Holding AG, Switzerland) or a Canon Aplio 400–700 system (Canon Medical Systems Europe BV, The Netherlands). In unit 2, cUS examinations were performed with an Aloka Alpha 7 system (Hitachi Medical Systems Holding AG). Both units used a multifrequency transducer, with a frequency of 8–11 MHZ. The routine cUS protocol in both units included serial examinations starting on the day of birth and repeated on day 3, 7, 14 and weekly thereafter until discharge or transfer to another hospital, complemented by examinations whenever deemed clinically relevant. Images were obtained using the anterior fontanel and recorded in at least six coronal and five sagittal planes. In addition, images via the mastoid fontanel were obtained to assess cerebellar growth and injury. All images were stored online and available for review and measurements (Clinical Assistant, RVC, The Netherlands). TCD was measured in all infants, preferably via the mastoid fontanel. If this was not possible, anterior fontanel images were used. In addition, biparietal diameter (BPD) and corpus callosum-fastigium length (CCFL) were measured on all cUS examinations (Fig. 1). All measurements were performed by the same researcher (L.A.W). As we found high intra- and inter-rater correlation coefficients in a previous study for all 3 measurements [32], a statistical analysis of uniformity among raters was not deemed necessary. For infants with corticosteroids, the number of days between the start of treatment and the last available cUS measurement was calculated.

Statistics

Baseline characteristics were compared between the dexamethasone, hydrocortisone, and control group using a t test for continuous data and a χ^2 test for categorical or ordinal data. A Mann-Whitney U test was used to compare Apgar scores between groups.

Linear mixed models were created for TCD, BPD, CCFL, and HC, respectively, adjusting for varying numbers and time points of measurements between infants. In these models, the last measurement before initiation of treatment and all measurements after the start of treatment were included. All measurements from the control group were included. The interactions of all significant factors were tested in various models but removed from the final model when these interactions were not significant. Measurements from the dexamethasone and hydrocortisone groups were compared to the control group separately to allow for adjustment using a propensity score [1] and compared to each other in an additional model [2]. For the comparison of one treatment group to the control group, dexamethasone or hydrocortisone use, PMA at measurement, sex, and HC z-score at birth were added as fixed effect parameters. In an additional analysis, we used logistic regression to calculate for each child a propensity score, indicating the likelihood of corticosteroid treatment as predicted by GA, birth weight z-score, sex, and duration of mechanical ventilation. This propensity score, an indicator of illness severity and reflecting baseline prognostic differences, was used for adjusting associations between treatment and outcome, based on the methods used by Rademaker et al. [33]. In the model comparing the two treatment groups, GA at birth and HC z-score at birth were chosen as fixed parameters next to PMA at measurement and type of treatment.

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Table 1. Baseline characteristics of the study population

	Control ($n = 241$)	Dexamethasone ($n = 68$)	p (D/C)	Hydrocortisone ($n = 37$)	p (H/C)	p (D/H)
Sex (female)	137 (56.8%)	30 (44.1%)	0.063	18 (48.6%)	0.350	0.656
Multiple gestation	88 (36.5%)	20 (29.4%)	0.278	9 (24.3%)	0.147	0.578
GA at birth, weeks	27.2 (1.1)	25.4 (1.0)*	<0.001	26.4 (1.1)*	<0.001	<0.001
Birth weight, g	959 (212)	761 (177)*	<0.001	802 (162)*	<0.001	0.242
Birth weight z-score	0.07 (0.88)	0.01 (0.77)	0.570	−0.21 (1.07)	0.081	0.242
HC at birth, mm	242 (17) *30 missing*	218 (14)* *14 missing*	<0.001	237 (11)	0.087	0.001
HC z-score at birth	−0.5 (1.0) *30 missing*	−0.9 (0.9)* *14 missing*	0.005	−0.1 (0.8)*	0.023	0.009
Apgar score 5 min[a]	8 (3) *4 missing*	7 (2)* *4 missing*	0.005	7 (2) *2 missing*	0.333	0.865
Necrotizing enterocolitis	13 (5.4%)	1 (1.5%)	0.169	2 (5.4%)	0.998	0.248
Patent ductus arteriosus[b]	76 (31.5%)	39 (57.4%)*	<0.001	17 (45.9%)	0.084	0.263
Sepsis	116 (48.1%)	43 (63.2%)*	0.028	17 (45.9%)	0.804	0.087
Intraventricular hemorrhage	61 (25.3%)	22 (32.4%)	0.247	12 (32.4%)	0.359	0.993
IVH grade 2	31 (12.8%)	12 (17.6%)	0.587	8 (21.6%)	0.602	0.868
IVH grade 3	7 (12.9%)	4 (5.9%)		1 (2.7%)		
Days on ventilator	6.9 (8.3) *1 missing*	23.6 (13.1)*	<0.001	18.9 (8.9)*	<0.001	0.052
Length of NICU admission, days	48.4 (18.3)	71.5 (28.8)*	<0.001	65.6 (18.7)*	<0.001	0.265
NICU mortality >28 days	2 (0.8%)	6 (8.8%)*	<0.001	2 (5.4%)*	0.030	0.528
Cumulative dose[a]		2.30 (0.98)		72.5[c]		
Start treatment PMA, weeks[a]		27.6 (2.3)		28.6 (2.4)		
Start treatment postnatal age, days[a]		15.0 (9.0)		14.0 (6.5)		
Number of TCD measurements[d]	893 (3)	231 (3)		150 (4)		
Number of BPD measurements[d]	1,465 (6)	356 (5)		232 (6)		
Number of CCFL measurements[d]	1,374 (5)	285 (4)		186 (5)		
Number of HC measurements[d]	1,363 (6)	428 (7)		160 (3)		

D/C, comparison of dexamethasone and control group; H/C, comparison of hydrocortisone and control group; D/H, comparison of dexamethasone and hydrocortisone group. *$p < 0.05$. Results are provided as n (%) or mean (SD) unless indicated otherwise. [a]Median (IQR). [b]Medical and surgical treatment. [c]Standard dose. [d]Total (median per infant).

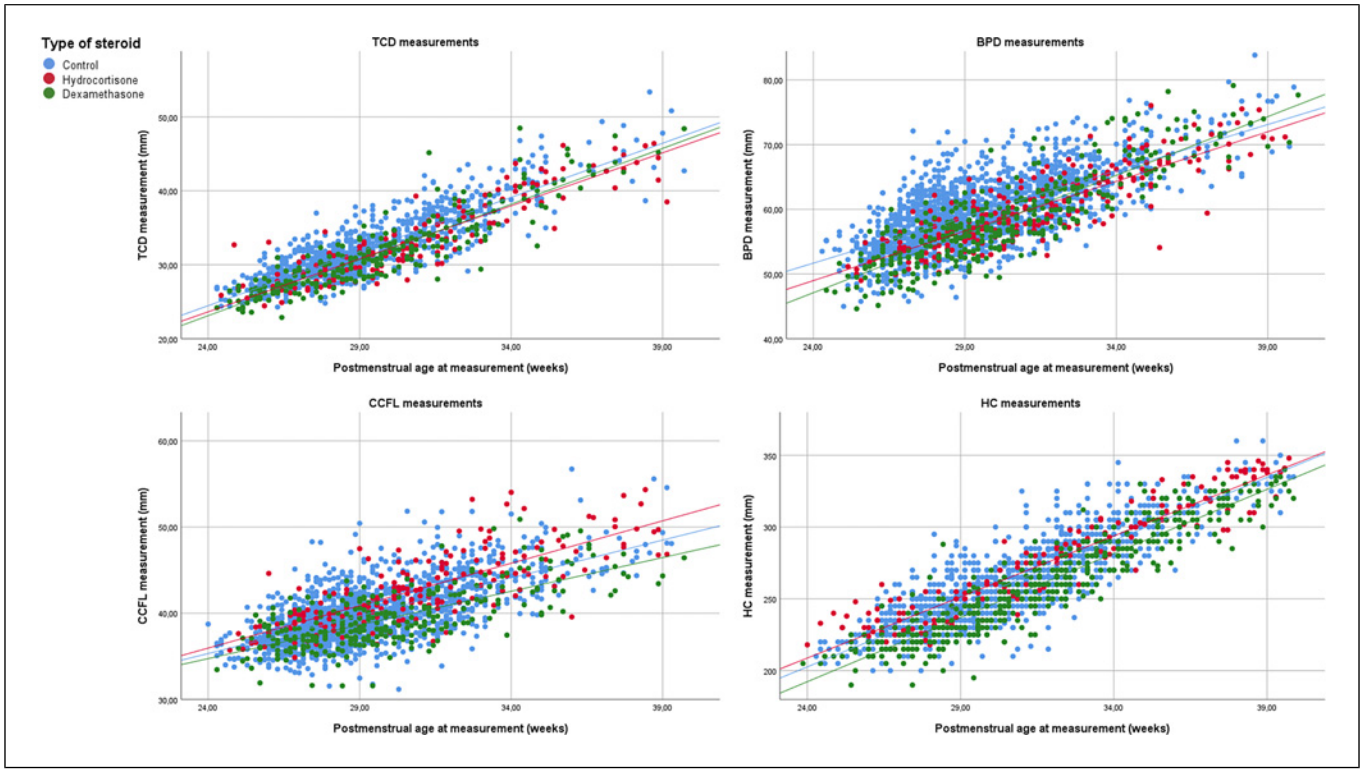

Fig. 2. TCD, BPD, CCFL, and HC measurements from the last measurement before the start of dexamethasone or hydrocortisone onward with all TCD, BPD, CCFL, and HC measurements in the control group plotted against PMA at measurement.

To assess whether a difference in cerebellar or cerebral growth could be attributed to the start of treatment, the last measurement before the start of corticosteroids for each infant in one of the treatment groups was selected and compared to a measurement at a comparable PMA in a control infant with similar GA at birth, and preferably also HC z-score at birth and sex. These measurements were compared using linear regression including the variables dexamethasone/hydrocortisone use, PMA at measurement, sex, HC z-score at birth, and propensity score. Statistical analyses were performed using IBM SPSS Statistics 25 for baseline characteristics and linear regression. R 4.0.3 was used to create linear mixed models.

Results

Patient Characteristics

In total, 346 infants were included. Antenatal steroids (betamethasone) were administered in approximately 85% of patients, according to national guidelines and similar in both centers. Dexamethasone and hydrocortisone groups differed significantly from the control group in several variables (Table 1). In addition, infants in the dexamethasone group were born at lower GA, with smaller HC and lower HC z-score at birth than the hydrocortisone group. Corticosteroid treatment was started at a median age of 15 days postnatally (Q1–Q3 12–19).

Brain Measurements

The number of measurements in the different groups and the median number of measurements per infant are provided in Table 1. Measurements are displayed in Figure 2. The median number of days between start of corticosteroid treatment and the last TCD measurement was 41 days (Q1–Q3 18–49) for the hydrocortisone group and 30 days (Q1–Q3 18–44) for the dexamethasone group.

Baseline Comparison

There were no differences between the treatment and control groups in TCD, BPD, and HC measurements performed before corticosteroid treatment was started. CCFL measurements did not differ between the dexamethasone and control group but were significantly larger in the hydrocortisone group compared to controls ($p = 0.008$). Adjustment for propensity score did not change the observed associations.

Table 2. Results of linear mixed models for TCD, BPD, CCFL, and HC from the last measurement before administration of glucocorticoid treatment onward (in mm)

	TCD in mm		BPD in mm		CCFL in mm		HC in mm	
	estimate (95% CI)	*p* value	estimate (95% CI)	*p* value	estimate (95% CI)	*p* value	estimate (95% CI)	*p* value
Dexamethasone								
No propensity score	−1.0 (−1.5; −0.5)*	<0.001	−1.8 (−2.8; −0.8)*	<0.001	−0.8 (−1.4; −0.2)*	0.008	−4.9 (−7.2; −2.6)*	<0.001
Propensity score	−0.9 (−1.6; −0.3)*	0.006	0.5 (−0.8; 1.8)	0.467	−0.4 (−1.2; 0.4)	0.315	−3.1 (−6.5; 0.3)	0.076
Hydrocortisone								
No propensity score	−1.4 (−1.9; −0.8)*	<0.001	−2.6 (−3.8; −1.5)*	<0.001	1.1 (0.4; 1.8)*	0.003	9.8 (8.7; 10.9)*	<0.001
Propensity score	−1.0 (−1.7; −0.3)*	0.004	−0.8 (−2.0; 0.5)	0.243	1.6 (0.8; 2.4)*	<0.001	3.1 (−0.3; 6.6)	0.075
Hydrocortisone compared to dexamethasone								
	−0.5 (−1.4; 0.4)	0.247	−2.1 (−3.5; −0.8)*	0.002	1.6 (0.6; 2.6)*	0.001	4.3 (−0.3; 9.0)	0.065

Measurements after Start of Corticosteroid Treatment

Table 2 shows linear mixed models created for TCD, BPD, CCFL, and HC in the dexamethasone and hydrocortisone groups compared to the control group and to each other. TCD ($p < 0.001$), BPD ($p < 0.001$), CCFL ($p = 0.008$), and HC ($p < 0.001$) growth were all slower in infants with dexamethasone. However, after adjusting for the propensity score, only TCD growth remained significantly slower in the dexamethasone group ($p = 0.006$). Infants who received hydrocortisone had slower TCD ($p = 0.003$) and BPD ($p < 0.001$) but faster CCFL ($p = 0.003$) and HC ($p < 0.001$) growth. After propensity score adjustment, TCD growth remained slower ($p = 0.004$) and CCFL growth faster ($p < 0.001$) without differences in BPD and HC growth. When comparing dexamethasone and hydrocortisone to each other, BPD ($p = 0.002$) growth was slower and CCFL ($p = 0.001$) growth faster in the hydrocortisone group. PMA and HC z-score at birth positively influenced all measurements. In addition, female sex was positively associated with BPD, CCFL, and HC measurements.

Discussion

This retrospective study showed that cerebellar growth was reduced in preterm infants who received dexamethasone or hydrocortisone for CLD compared to preterm infants who received no postnatal corticosteroids. The negative association of both types of corticosteroids was not seen on cerebral growth.

Cerebellar Measurements

The mixed model analysis displayed a statistically significant relationship between TCD and both dexamethasone and hydrocortisone treatment. The similarity in effect sizes indicates that these treatments may have similar negative associations with cerebellar growth. The model comparing both treatment types to each other confirmed this, showing no difference between the two groups. TCD in both treatment groups before start of treatment did not differ from TCD in controls, thus indicating that the observed differences occurred after initiation of treatment.

Parikh et al. [20] reported the cerebellar volume to be smaller in extremely low birth weight infants who received dexamethasone (cumulative mean dose 2.8 mg/kg, mean duration 6.8 days) compared to infants who had not received corticosteroids. However, they included only 41 infants of whom 11 received dexamethasone, used one time point (term-equivalent age) to measure the volume, and dexamethasone was only given after 28 days postnatally. As this was an MRI study, 3D cerebellar volume was measured, and we performed 2D linear measurements on cUS where the results are not directly comparable, although both studies indicate an effect on cerebellar size. Tam et al. [21] also reported similar results: cerebellar volumes were smaller on MRI at term-equivalent age in 17 preterm infants with dexamethasone (cumulative median dose 0.89 mg) compared to 115 preterm infants without dexamethasone. Lastly, Cuzzilla et al. [22] performed a prospective cUS study in 144

infants born <30 weeks' GA and also found reduced cerebellar growth in 18 infants receiving dexamethasone in an unknown dose and duration. The relationship between reduced cerebellar growth and initiation of dexamethasone treatment was not examined in these studies. The results concerning dexamethasone in the present study with a larger population are in agreement with the abovementioned results and provide information regarding the relationship between initiation of treatment and decreased growth.

Tam et al. [21] also reported smaller cerebellar volumes on MRI in 25 preterm infants with hydrocortisone compared to 57 infants without postnatal corticosteroids, albeit a smaller difference than for dexamethasone and with a lower dose of hydrocortisone (cumulative median dose 11.58 mg) than in the present study. Benders et al. [34], however, showed no smaller cerebellar volume on MRI at term-equivalent age in 19 hydrocortisone-treated preterm infants compared to 19 controls. Likewise, Kersbergen et al. [35] found no difference between 73 hydrocortisone-treated preterm infants and 73 matched controls regarding cerebellar volume on MRI at term-equivalent age. The last two studies used the same hydrocortisone regimen as this study. In addition, Parikh et al. [36] performed a randomized study in extremely low birth weight infants, showing a lack of difference in cerebellar volume on MRI at term-equivalent age in 31 hydrocortisone-treated infants compared to 33 placebo-treated infants, although the cumulative hydrocortisone dose (17 mg/kg over 7 days) was considerably lower than that in our and other studies. Regarding these results, the negative association found in the present study is notable. Differences in cumulative dose, the number of measurements, and three-dimensional as opposed to linear measurements may partly explain this difference in results.

Cerebral Growth

To assess whether cerebral growth was affected by corticosteroid treatment, BPD, CCFL, and HC measurements were performed. Dexamethasone had a significant negative association with BPD, CCFL, and HC growth after the start of treatment, and hydrocortisone was associated with a significant reduction in BPD growth. However, these associations all disappeared when adjusting for propensity score. CCFL and HC measurements were larger in the hydrocortisone group than in the control group, of which only the larger CCFL measurements remained in the adjusted model. These results indicate that illness severity rather than dexamethasone or hydrocortisone treatment affected cerebral growth. This is in concordance with results from a study by Rousseau et al. [37], indicating that other perinatal factors than postnatal hydrocortisone are more influential in determining cerebral growth, although earlier studies did report impaired cerebral growth and development associated with postnatal corticosteroids [6–9, 37]. The differential results as compared to cerebellar measurements might be explained by a varying vulnerability of specific cell types in various central nervous system regions, such as the specific vulnerability of cerebellar neurons during a crucial phase of development. During the second half of gestation, the cerebellum grows more rapidly than any other brain structure. It also contains the largest number of glucocorticoid receptors in the developing brain, localized in the external granular layer. In animal models, systemic treatment with glucocorticoids resulted in decreased proliferation and increased apoptosis of the granule cells of the external granular layer and this can negatively impact cerebellar growth [21]. In preterm infants, postnatal corticosteroids are often initiated around 27–28 weeks, which is an important period of accelerated cerebellar growth. Larger CCFL measurements in infants who were born more prematurely have been reported before [32]. This difference might be related to different head shapes as a result of positioning of the infant. As infants with hydrocortisone were younger at birth and born at another center, this may partially explain the results in this group. Lastly, BPD, CCFL, and HC measurements were positively affected by female sex. In the context of larger measurements for regional brain volumes for male infants, these results may indicate a stronger association of corticosteroids with cerebral growth in male infants compared to females [38].

Limitations

The study has several limitations. First, due to its retrospective design, not all cUS examinations were of sufficient quality to perform reliable measurements. However, cUS examinations were performed routinely, by trained sonographers, following standard protocols in this population. Furthermore, the number of measurements per patient varied due to length of stay and a slight difference in cUS protocols in both centers. For cerebellar measurements, however, the number of measurements did not differ between the treatment and control groups. Prospective studies could improve both the number of measurements and image quality. A second limitation is that both cerebellar and cerebral growth may be influenced by illness of infants who need dexamethasone or hydrocortisone treatment. A propensity score was used to adjust for this difference, but factors that are not

accounted for in this score might still be a source of bias. This is mainly a concern for aspects of illness severity which are difficult to identify or quantify, such as the frequency of apnea and bradycardia, hypoxia, and punctate cerebellar hemorrhage which are too small to be seen on cUS examinations. In addition, supratentorial hemorrhage could negatively influence cerebellar growth, although infants with complicated intraventricular hemorrhage were excluded from this study population. For the comparison between hydrocortisone and dexamethasone and the effects on brain growth, it is important to mention that the cumulative hydrocortisone dose was higher than the calculated equivalent dexamethasone dose, and that hydrocortisone was given over a longer period (21 days instead of 16 days dexamethasone). Still both treatments were provided according to the national guidelines and therefore standard of care. Lastly, the hydrocortisone group was relatively small, and these patients were admitted to another NICU than the dexamethasone-treated infants and all controls. Difference in centers and their standard practices could therefore contribute to the results as reported for the hydrocortisone group.

Conclusion

Administration of dexamethasone or hydrocortisone in premature infants with respiratory failure is associated with a significant reduction in cerebellar growth, seen after onset of corticosteroid administration, while cerebral growth was not affected. This comparison has, to our knowledge, never been shown before with this large number of sequential measurements. The observations could be explained by a very specific vulnerability in the preterm cerebellum during a rapid and crucial phase of development. Prospective studies, using serial imaging and if possible volumetric MRI, are needed to confirm these relationships. In addition, alternative treatments for CLD should be studied to explore opportunities to prevent immediate and long-term harmful effects of corticosteroids. Moreover, dose-dependent effects deserve attention. Until then, restrictive policies concerning corticosteroid administration seem appropriate.

Statement of Ethics

As this study did not fall under the Medical Research Involving Human Subjects Act, clinically obtained pseudonymized data were used, the medical ethical committees of the participating centers (Medical Ethics Committees Leiden Den Haag Delft and Isala Zwolle) waived the need for ethics approval and informed consent. Reference number G 20.177.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Laura A. Warmerdam contributed to design, methodology, investigation, data curation, formal analysis, and drafting the initial manuscript of this study. Gerda van Wezel-Meijler contributed to investigation, supervision, and reviewing the manuscript of this study. Linda S. de Vries contributed to design, supervision, and reviewing the manuscript of this study. Floris Groenendaal contributed to methodology, formal analysis, and reviewing the manuscript of this study. Sylke J. Steggerda contributed to design, methodology, investigation, data curation, formal analysis, supervision, and reviewing the initial manuscript of this study.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy concerns. Requests for data availability can be made via the corresponding author.

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