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Alison, Marianne; Tilea, Bogdana; Toumazi, Artemis; Biran, Valérie; Mohamed, Damir; Alberti, Corinne; Bourmaud, Aurélie; Baud, Olivier

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Marianne Alison,[1] Bogdana Tilea,[1] Artemis Toumazi,[1] Valérie Biran,[2,3] Damir Mohamed,[4] Corinne Alberti,[4] Aurélie Bourmaud,[1] Olivier Baud ,[3,5] for the PREMILOC Trial group

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[1]Pediatric Radiology, Hôpital Universitaire Robert Debré, Paris, France
[2]Neonatal Intensive Care Unit, Hopital Universitaire Robert Debre, Paris, Île-de-France, France
[3]Inserm U1141, University of Paris, Paris, France
[4]Centre d'Investigation Clinique-Epidémiologie Clinique, Hopital Universitaire Robert Debre, Paris, France
[5]DFEA, Hôpitaux Universitaires de Genève, Geneva, Switzerland

Correspondence to
Dr Olivier Baud, DFEA, Hôpitaux Universitaires de Genève, Geneva 1211, Switzerland; olivier.baud@hcuge.ch

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ABSTRACT

Objective To determine whether early low-dose hydrocortisone treatment in extremely preterm infants is associated with brain damage assessed by MRI at term equivalent of age (TEA).

Patients and outcomes This is a predefined secondary analysis of brain abnormalities, observed by MRI at TEA, of patients randomly assigned to receive either placebo or hydrocortisone in the PREMILOC trial. Outcomes were based on brain abnormalities graded according to Kidokoro scores.

Results Among 412 survivors at TEA, 300 MRIs were performed and 295 were suitable for analysis. Kidokoro scoring was completed for 119/148 and 110/147 MRIs in the hydrocortisone and placebo groups, respectively. The distribution of the Kidokoro white matter (WM) subscore and other subscores was not significantly different between the two groups. There was, however, a significant association between a higher overall Kidokoro score and hydrocortisone treatment (5.84 (SD 3.51) for hydrocortisone and 4.98 (SD 2.52) for placebo; mean difference, 0.86; 95% CI 0.06 to 1.66; p=0.04). However, hydrocortisone was not statistically associated with moderate-to-severe brain lesions (Kidokoro overall score ≥6) in a multivariate logistic regression model accounting for potential confounding variables (adjusted OR (95% CI) 1.27 (0.75 to 2.14), p=0.38). Bronchopulmonary dysplasia at 36 weeks postmenstrual age significantly predicted both WM damage (adjusted OR (95% CI) 2.70 (1.03 to 7.14), p=0.04) and global brain damage (adjusted OR (95% CI) 2.18 (1.19 to 3.99), p=0.01).

Conclusions Early hydrocortisone exposure in extremely preterm infants is not statistically associated with either WM brain damage or overall moderate-to-severe brain lesions when adjusted for other neonatal variables.

Trial registration number EudraCT number 2007-002041-20, NCT00623740

What is already known on this topic?

► Selective postnatal hydrocortisone is not associated with either brain injury or a reduction in brain volume by MRI at term-equivalent of age in cohort studies. Prophylactic postnatal hydrocortisone is associated with increased bronchopulmonary dysplasia (BPD)–free survival.

What this study adds?

► Prophylactic low-dose hydrocortisone is not associated with a statistically significant higher incidence of brain damage by MRI when adjusted for other neonatal variables. BPD is an independent predictor of brain damage by MRI in extremely preterm infants.

INTRODUCTION

The improving survival of extremely premature infants over the past decades has led to an increasing number of infants developing bronchopulmonary dysplasia (BPD), resulting in neonatal brain injury and subsequent neurodevelopmental impairment.[1 2] These complications have been shown to be related to systemic inflammation.[3 4] Postnatal dexamethasone therapy has been found to confer short-term benefits gained at the expense of impaired brain growth, principally affecting the cerebral cortical grey matter (GM),[5] and an increased incidence of adverse neurodevelopmental events.[6] Recently, the PREMILOC clinical trial tested early low-dose hydrocortisone as an alternative treatment, with potentially fewer neurodevelopmental consequences, in infants born extremely preterm at high risk of BPD. This trial showed a significant improvement in the rate of BPD-free survival at 36 weeks postmenstrual age (PMA),[7] without detectable adverse neurodevelopmental outcomes at 2 years of age in hydrocortisone-treated infants.[8 9] Although definitive proof of the neurodevelopmental safety of hydrocortisone requires further long-term assessment, early prediction of neurodevelopmental outcomes of very immature infants is still a critical point in prognostic discussions with families of infants born very preterm. MRI at term equivalent of age (TEA) allows the detection of structural abnormalities associated with encephalopathy of prematurity,[10] characterised by white matter (WM) and GM damage.[11] Several studies have shown that brain abnormalities detected by MRI are strong neonatal predictors of long-term outcomes,[12 13] notably general intellectual and specific learning disabilities.[14] MRI findings at TEA are therefore highly useful in confirming the reassuring neurological assessment already performed at 2 years of age, and before further clinical assessment of infants exposed to hydrocortisone will be completed at

Table 1 Perinatal and neonatal characteristics of infants with MRI performed at term equivalent of age

Variable	Hydrocortisone n=148	Placebo n=147
Birth weight (g)		
Median (IQR)	860 (750–970)	880 (760–1000)
Minimum; maximum	597; 1290	565; 1345
Gestational age at birth (weeks)		
Median (IQR)	26.4 (25.9–27.1)	26.7 (26.0–27.1)
Minimum; maximum	24.6; 27.9	24.3; 27.9
Male sex, N (%)	71 (48%)	86 (59%)
Multiple pregnancy, N (%)	49 (33%)	52 (35%)
Antenatal steroids, N (%)	144 (97%)	143 (97%)
Histological chorioamnionitis	n=139	n=137
N (%)	71 (51%)	76 (55%)
Prolonged premature rupture of membranes, N (%)	45 (30%)	56 (38%)
Caesarean section, N (%)	69 (47%)	64 (43%)
BPD at 36 weeks PMA, N (%)	41 (28%)	50 (34%)
Surgery for PDA, N (%)	24 (16%)	32 (22%)
Late-onset sepsis, N (%)	44 (30%)	35 (24%)
Necrotising enterocolitis, N (%)	9 (6%)	9 (6%)
Intestinal perforation, N (%)	4 (3%)	4 (3%)
Intraventricular haemorrhage grades 3–4, N (%)	11 (7%)	13 (9%)

BPD, bronchopulmonary dysplasia; PMA, postmenstrual age; PDA, patent ductus arteriosus.

preschool age. This study compared the extent of brain abnormalities by MRI at TEA in infants enrolled in the PREMILOC trial who received either postnatal early low-dose hydrocortisone or placebo.

PATIENTS AND METHODS

Population and study protocol

All infants recruited in the PREMILOC trial and alive at TEA were eligible for brain MRI. The study protocol has been described previously.[7] Briefly, this double-blind, multicentre, randomised, placebo-controlled trial enrolled inborn infants born between $24^{0/7}$ and $27^{6/7}$ weeks of gestation before 24 hours postnatal age and randomly assigned them to receive either placebo or hydrocortisone (1 mg/kg/day divided into two doses per day for 7 days, followed by 0.5 mg/kg/day for 3 days). Randomisation was stratified by gestational age (24–25 and 26–27 weeks of gestation).

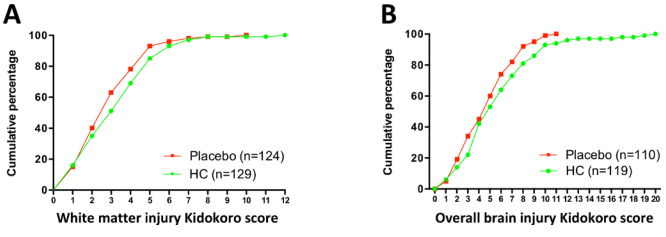

Figure 1 Cumulative distribution of white matter injury (A) and overall brain injury (B) Kidokoro scores assessed by MRI at term equivalent of age in infants exposed to placebo or early low-dose hydrocortisone (HC).

Brain imaging and MRI scoring

All examinations were performed using a 1.5 T MRI with standard head coil, without sedation, during the post-feed period. Parameters of T1, T2, T2 GE used in this study are described in online supplementary methods. A standardised scoring system was used to evaluate cerebral WM, cortical and deep GM, and cerebellar abnormalities, as described in Kidokoro *et al*.[15] The presence of haemorrhagic lesions was analysed as described in Papile *et al*.[16] The following quantitative biometric values were measured: lateral ventricular diameter on a coronal slice at the level of the ventricular atrium, biparietal width and interhemispheric distance between the crown of the superior frontal gyri on a coronal slice using the bilateral cochlea and basilar truncus as landmarks, deep GM area measured on an axial slice in which caudate heads, lentiform nuclei and thalami were maximally visible, largest transcerebellar diameter measured on a coronal slice at the level of the ventricular atrium, and vermian height and anteroposterior diameter measured on a midsagittal view.

All data were transferred to a post-processing tool (IntelliSpace Portal; Philips Healthcare) for analysis by the same paediatric radiologist with 13 years of experience, unaware of the treatment group.

The primary endpoint of the study was the estimated occurrence of cerebral WM abnormalities graded based on five variables based on the Kidokoro subscore: cystic lesion, focal signal abnormalities, delayed myelination, dilated lateral ventricles and reduced biparietal width measured on a coronal slice (online supplementary table 1). The total cerebral WM score was reported as cumulative percentages and categorised as normal/subnormal (0–1) or abnormal (≥2). Thinning of the corpus callosum was not included in the WM scoring because it was not considered to be sufficiently reliable in our study based on 3 mm thick slices.

Cortical GM abnormality was graded based on three variables: signal abnormality, gyral maturation (including tertiary inferior temporal and inferior occipital gyri and sulci as normal markers at TEA) and increased extracerebral space. Deep GM and cerebellum scores were graded based on signal abnormalities and volume reduction.

An overall brain abnormality score was calculated as the sum of the four regional subscores, categorised as normal-to-mild (0–5) and moderate-to-severe (≥6), and reported as cumulative percentages.

The secondary endpoint of this study was to investigate and analyse the potential factors associated with the severity of the WM injury score or the overall brain injury score.

Statistical analysis

The Shapiro-Wilk test was used at baseline to determine whether the data were normally distributed. Continuous variables are reported as means with SD for normal data or medians with IQRs for non-normal data. Categorical data are presented as frequencies with percentages.

Treatment groups were compared using χ^2 test for categorical variables. Independent samples t-tests or non-parametric Mann–Whitney–Wilcoxon tests were used to compare continuous variables, depending on their distribution.

Quantitative analyses were performed on the Kidokoro scores for WM damage and global brain damage. Cumulative distributions and the mean differences (with 95% CI) were reported and compared using a t-test between the two treatment groups.

For the secondary outcome, a logistic regression analysis was performed on the entire study population of examined patients

Table 2 White matter damage according to treatment and gestational age group

	24–25 weeks n=74		26–27 weeks n=221		Total n=295	
Variable	Hydrocortisone n=39	Placebo n=35	Hydrocortisone n=109	Placebo n=112	Hydrocortisone n=148	Placebo n=147
Focal signal abnormality	n=39	n=32	n=106	n=110	n=145	n=142
N (%)	12 (31%)	9 (29%)	45 (42%)	38 (35%)	57 (39%)	47 (33%)
Cystic lesions, N (%)	n=39	n=35	n=108	n=111	n=147	n=146
Total	3 (8%)	2 (6%)	9 (8%)	2 (2%)	12 (8%)	4 (3%)
Focal	3	1	4	1	7	2
Extensive	0	1	5	1	5	2
Myelination delay	n=37	n=35	n=103	n=106	n=140	n=141
N (%)	5 (14%)	7 (20%)	16 (16%)	18 (17%)	21 (15%)	25 (18%)
Dilated lateral ventricle	n=33	n=31	n=98	n=104	n=131	n=135
N (%)	11 (33%)	20 (65%)	51 (52%)	47 (45%)	62 (47%)	67 (50%)
Right lateral ventricle (mm)	n=33	n=31	n=102	n=106	n=135	n=137
Median (IQR)	6.6 (5.6–7.6)	7.3 (6.0–9.2)	7.0 (6.0–8.1)	6.4 (5.7–7.8)	7.0 (5.8–8.0)	6.7 (5.8–7.9)
Minimum; maximum	3.0; 10.5	3.9; 13.1	3.8; 31.0	3.2; 13.0	3.0; 31.0	3.2; 13.1
Left lateral ventricle (mm)	n=33	n=31	n=101	n=106	n=134	n=137
Median (IQR)	6.6 (5.7–8.2)	7.8 (6.4–8.7)	7.4 (6.1–8.6)	7.0 (5.9–8.1)	7.1 (6.1–8.4)	7.2 (6.0–8.3)
Minimum; maximum	4.5; 13.0	4.6; 17.3	3.7; 16.3	4.5; 13.6	3.7; 16.3	4.5; 17.3
Volume reduction	n=33	n=31	n=102	n=106	n=135	n=137
N (%)	16 (48%)	18 (58%)	52 (51%)	58 (55%)	68 (50%)	76 (55%)
Biparietal diameter (mm)	n=33	n=31	n=102	n=106	n=135	n=137
Median (IQR)	78.0 (73.4–80.5)	76.1 (73.2–80.7)	76.8 (72.1–80.3)	75.5 (73.1–81.4)	76.8 (72.6–80.5)	75.6 (73.1–80.7)
Minimum; maximum	60.8; 91.9	63.1; 88.6	66.7; 88.6	66.0; 89.9	60.8; 91.9	63.1; 89.9

to analyse the relationship between the primary outcome (WM score ≥2), treatment group (hydrocortisone vs placebo) and baseline characteristics known to be associated with brain injury (antenatal steroids, delivery route, sex, late-onset sepsis, BPD at 36 weeks PMA) and adjusted for the gestational age group. An additional study of factors associated with an overall Kidokoro score ≥6, as a marker of moderate-to-severe brain damage, was performed using the same analysis. ORs and their 95% CIs were computed. Variables statistically associated at a significance level of 20% in the univariate analysis were included in a multivariate model. The final significant variables in the multivariate analyses were those with p values <0.05 (stepwise selection). Multicollinearity between the potential predictor variables was tested before performing the two logistic regression analyses.

All the statistical analyses were performed using SAS software V.9.4 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

Of the 523 infants randomised in the PREMILOC trial, 414 (79.2%) survived to TEA. Among surviving infants, 300/414 (72.5%) had a brain MRI, of which the scans of five infants were of insufficient quality (online supplementary figure 1). The analysis of brain MRI was therefore performed on 295 infants with good-to-excellent quality scans for conventional sequences (n=148 in the hydrocortisone group and n=147 in the placebo group). Baseline and neonatal characteristics of the 300 infants with brain MRI and the 221 infants included in the trial who did not have an MRI are summarised in online supplementary table 2. The perinatal and neonatal characteristics of patients assessed by MRI were similar between the two treatment groups (table 1). In particular, we found no statistically significant differences in antenatal steroid exposure, the incidence of chorioamnionitis, sex ratio, or the occurrence of major neonatal complications between the two groups. The distributions of the global Kidokoro score and subscores, according to treatment and gestational age groups, are summarised in online supplementary table 3.

WM damage at TEA according to treatment in each gestational age group

Quantitative analysis of the cumulative distribution of WM scores for the hydrocortisone and placebo groups showed no statistically significant association with treatment group (mean score, 3.59 (SD 2.03) for hydrocortisone and 3.23 (SD 1.73) for placebo; mean difference 0.36; 95% CI −0.10 to 0.83; p=0.13) (figure 1A). The major abnormalities associated with WM damage, according to treatment and gestational age group, are summarised in table 2 and the frequencies were found to be similar. However, fewer infants born at 24 to 25 weeks in the hydrocortisone group developed dilated lateral ventricles at TEA than in the placebo group (11/33 (33%) vs 20/31 (65%), p=0.02; table 2). Similarly, the lateral ventricle in the hydrocortisone group was smaller than that in the placebo group. In contrast, more infants born at 26 to 27 weeks in the hydrocortisone group developed cystic lesions than those in the placebo group (9/108 (8.3%) vs 2/111 (1.8%), p=0.03; table 2).

GM and other brain damage at TEA according to treatment in each gestational age group

The main abnormalities associated with the cortical and basal ganglia GM and cerebellar injury detected in MRI at TEA are summarised in table 3, as well as evidence of intraventricular haemorrhage. None of these variables showed differences between the two treatment groups. Analysis of the distribution of each subscore failed to show any statistically significant

Table 3 Grey matter brain damage, cerebellar damage and intraventricular haemorrhage detected by MRI according to treatment and gestational age group

	24–25 weeks n=74		26–27 weeks n=221		Total n=295	
Variable	Hydrocortisone n=39	Placebo n=35	Hydrocortisone n=109	Placebo n=112	Hydrocortisone n=148	Placebo n=147
Focal cortical signal abnormality, N (%)	n=37 0	n=32 0	n=105 0	n=110 0	n=142 0	n=142 0
Gyration delay >2 weeks, N (%)	n=38 0	n=34 2 (6%)	n=102 5 (5%)	n=109 3 (3%)	n=140 5 (4%)	n=143 5 (3%)
Enlarged pericerebral space, N (%)	n=33 14 (42%)	n=31 11 (36%)	n=102 50 (49%)	n=105 42 (40%)	n=135 64 (47%)	n=136 53 (39%)
Pericerebral space quantification (mm)	n=33	n=31	n=102	n=105	n=135	n=136
Median (IQR)	4.5 (3.5–6.0)	3.7 (3.1–5.6)	4.8 (3.3–6.4)	4.4 (3.4–5.8)	4.7 (3.3–6.2)	4.3 (3.4–5.8)
Minimum; maximum	2.4; 8.6	2.0; 11.8	1.6; 9.7	0.9; 10.8	1.6; 9.7	0.9; 11.8
Focal basal ganglia focal abnormality, N (%)	n=38 0	n=34 0	n=107 5 (5%)	n=111 2 (2%)	n=145 5 (3%)	n=145 2 (1%)
Basal ganglia volume reduction, N (%)	n=34 10 (29%)	n=28 13 (46%)	n=98 24 (24%)	n=97 22 (23%)	n=132 34 (26%)	n=125 35 (28%)
Basal ganglia surface (mm^2)	n=34	n=28	n=98	n=97	n=132	n=125
Median (IQR)	10.2 (9.4–10.9)	9.8 (9.1–10.8)	10.2 (9.5–11.1)	10.6 (9.7–11.4)	10.2 (9.4–11.0)	10.4 (9.4–11.3)
Minimum; maximum	8.1; 13.1	7.2; 11.8	6.7; 14.7	6.5; 23.1	6.7; 14.7	6.5; 23.1
Cerebellar signal abnormality, N (%)	n=38 4 (11%)	n=35 4 (11%)	n=107 12 (11%)	n=111 6 (5%)	n=145 16 (11%)	n=146 10 (7%)
Cerebellar transverse diameter (mm)	n=33	n=29	n=100	n=106	n=133	n=135
Median (IQR)	51.3 (48.8–53.0)	49.7 (48.9–53.5)	51.7 (49.1–54.5)	52.1 (49.2–53.7)	51.6 (49.0–54.2)	51.9 (49.0–53.7)
Minimum; maximum	31.2; 66.8	41.6; 58.7	38.0; 68.2	40.2; 64.2	31.2; 68.2	40.2; 64.2
Vermis anteroposterior diameter (mm)	n=24	n=15	n=64	n=73	n=88	n=88
Median (IQR)	14.0 (12.6–15.5)	13.4 (12.1–14.6)	14.4 (13.1–15.6)	14.3 (13.4–15.5)	14.3 (13.0–15.6)	14.2 (13.2–15.5)
Minimum; maximum	9.3; 16.7	10.6; 17.9	8.5; 20.6	11.0; 20.1	8.5; 20.6	10.6; 20.1
Vermis height (mm)	n=24	n=15	n=64	n=72	n=88	n=87
Median (IQR)	23.5 (21.5–26.2)	24.0 (21.5–25.1)	23.7 (21.8–24.9)	23.4 (22.1–25.5)	23.6 (21.6–25.0)	23.4 (21.9–25.4)
Minimum; maximum	13.1; 29.1	18.8; 28.8	16.6; 34.1	19.9; 31.3	13.1; 34.1	18.8; 31.3
Intraventricular haemorrhage, N (%)	n=34	n=31	n=89	n=98	n=123	n=129
Any grades	19 (56%)	21 (68%)	41 (46%)	31 (32%)	60 (49%)	52 (40%)
Grade 1	9	9	17	17	26	26
Grade 2	7	10	15	13	22	23
Grade 3	0	2	7	0	7	2
Grade 4	0	0	2	1	2	1

association with treatment group for both the overall population and within gestational age groups (online supplementary figure 2).

Analysis of the cumulative distribution of the overall Kidokoro brain injury scores showed a statistically significant association between the score and treatment group (5.84 (SD 3.51) for hydrocortisone and 4.98 (SD 2.52) for placebo, mean difference, 0.86, 95% CI 0.06 to 1.66, p=0.04) (figure 1B). However, hydrocortisone treatment was no longer associated with either WM damage (WM injury score ≥2) or overall moderate-to-severe brain damage (brain injury overall score ≥6) after adjustment for several risk factors of brain damage and gestational age group (table 4).

Neonatal characteristics associated with brain damage at TEA

We also investigated the ability of recognised risk factors of brain vulnerability to predict brain damage using a logistic regression model (table 4). The most significant independent variables (20% significance level in univariate analysis and not showing multicollinearity) were added to the multivariate model adjusted for gestational age, in weeks, by stepwise selection. BPD at 36 weeks of PMA was found to be the only variable significantly associated with both the WM injury score (OR adjusted for gestational age group, 2.70; 95% CI 1.03 to 7.14; p=0.04) and overall brain injury score (OR adjusted for gestational age group, 2.18; 95% CI 1.19 to 3.99; p=0.01).

DISCUSSION

We measured the extent of brain abnormalities by MRI performed at TEA in surviving participants in this analysis of a predefined secondary outcome of the PREMILOC randomised trial. Hydrocortisone treatment given during the first 10 postnatal days to infants born extremely prematurely was not associated with statistically significant changes in the occurrence of WM or GM abnormalities or changes in biometric characteristics. Although we found a significant association between early hydrocortisone treatment and a higher overall Kidokoro brain injury score, this difference was no longer significant when brain abnormalities were categorised as minimal or mild (<6) and moderate to severe (≥6). These results are consistent with a logistic multiple regression analysis showing that hydrocortisone

Table 4 Logistic regression models for the association between perinatal/neonatal outcomes and brain damage

	White matter score ≥2 (n=253)		Kidokoro overall score ≥6 (n=228)	
Variable	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Logistic regression univariate model				
Treatment				
Placebo	1		1	
Hydrocortisone	1.08 (0.54 to 2.16)	0.83	1.27 (0.75 to 2.14)	0.38
Gestational age strata				
24–25 weeks	1		1	
26–27 weeks	1.00 (0.44 to 2.25)	1	1.31 (0.70 to 2.43)	0.4
Sex				
Male	1		1	
Female	1.12 (0.56 to 2.23)	0.76	0.83 (0.49 to 1.41)	0.49
Antenatal steroids				
No	1		1	
Yes	0.50 (0.06 to 4.00)	0.51	1.11 (0.33 to 3.75)	0.86
Delivery mode				
Vaginal	1		1	
C-section	0.78 (0.39 to 1.57)	0.48	1.20 (0.71 to 2.03)	0.51
Severe sepsis				
No	1		1	
Yes	0.76 (0.35 to 1.65)	0.49	0.98 (0.53 to 1.82)	0.94
BPD at 36 weeks PMA				
No	1		1	
Yes	2.08 (0.88 to 5.00)	0.1	2.20 (1.24 to 3.91)	0.007
Logistic regression multivariate model*				
BPD at 36 weeks PMA				
No	1		1	
Yes	2.70 (1.03 to 7.14)	0.04	2.18 (1.19 to 3.99)	0.01

*Adjusted for gestational age, in weeks.
BPD, bronchopulmonary dysplasia; PMA, postmenstrual age.

was not statistically associated with either WM damage or moderate-to-severe brain lesions.

These findings are in accordance with those of previous reports, showing that selective neonatal hydrocortisone treatment using higher doses (starting dose of 5 mg/kg/day tapered over a minimum of 3 weeks) had no detectable long-term effects on either neurostructural brain development at TEA, brain growth or neurocognitive outcomes at preschool age.[17–20] They are also consistent with 2-year clinical outcomes of the population recruited in the trial, demonstrating that early low-dose hydrocortisone treatment was not associated with a statistically significant difference in neurodevelopment at 2 years of age.[8 9] While waiting for preschool-age clinical assessment, the present data add further reassuring evidence supporting the neurodevelopmental safety of hydrocortisone use in extremely preterm infants, in particular in terms of the vulnerability of WM to postnatal steroids.[21]

We analysed the association between the global Kidokoro score of brain damage and hydrocortisone treatment by comparing cumulative distributions and moderate-to-severe damage between the two groups and by using a logistic regression model. We found statistically significant differences in the cumulative distributions but not in the regression model adjusted for potential confounders. This discrepancy may be due to the higher survival rate conferred by hydrocortisone, especially in premature participants born at 26 to 27 weeks,[7] leading to a higher number of surviving subjects exposed to comorbidities for the risk of brain injury. This hypothesis cannot be confirmed using competing risk analysis for death because this exploratory endpoint was based on a score measured at a single time point for each participant (at TEA) and studied in the survival population.

Although the detection of brain injury in extremely preterm newborns generally focuses on supratentorial injury, the cerebellum has been shown to be highly vulnerable in this population of patients, with potential detrimental effects of glucocorticosteroids and a substantial impact on long-term neurological outcome.[22] Tam *et al* reported a negative effect of hydrocortisone on cerebellar growth, with a decreased growth velocity during the early postnatal period, translating to a 10% decreased volume by TEA.[23] Here, we found no difference in the biometric characteristics or signal abnormalities in the cerebellum depending on hydrocortisone exposure, but the dose used in the PREMILOC trial was lower than that used in previous studies. Nevertheless, the MRI techniques used in this study are not suitable to assess the effect of treatment at the microstructural level. We cannot exclude a cytotoxic effect of hydrocortisone on proliferating cerebellar granule neuron precursor cells, as previously reported in neonatal mouse pups.[24]

The absence of a deleterious effect of hydrocortisone in extremely preterm infants is in contrast to the deleterious effect of postnatal dexamethasone reported in several studies, which persists to adolescence.[5 21 25] This discrepancy can be explained by the characteristics of hydrocortisone, including lower cortisol-equivalent dosage, its mineralocorticoid-mediated activity and shorter half-life in the brain due to specific inactivation by 11-β-hydroxysteroid dehydrogenase type 2, which is highly expressed in the fetal brain and enables the degradation of hydrocortisone.[20]

Another finding of this study is the statistically significant association between BPD at 36 weeks PMA and MRI abnormalities at TEA in infants surviving extremely preterm birth, for both WM and overall brain damage. Only one previous study addressed this question in very preterm infants and showed that delayed structural brain maturation assessed by MRI at TEA was preceded by BPD.[26] Here, we show that BPD is statistically associated with both WM damage and overall brain injury scores in a large population of extremely preterm infants, by univariate analyses and also when adjusted for several perinatal confounders for the brain maturation trajectory. However, although statistically associated, these findings do not prove a causal link between BPD and brain damage but more likely reflect a hidden confounder, that is, severe inflammation.

The main strength of this secondary analysis was the high proportion of enrolled patients who had access to MRI very close to the TEA, limiting the selection bias. However, this study also had several limitations. The main limitation was its being underpowered to detect any adverse effect of hydrocortisone on rare severe cerebral lesions, as the Kidokoro scores showed a large majority of the infants to have minimal or mild injury. We did not use a correction for multiple comparisons to avoid increasing the likelihood of type II error (true differences deemed not to be significant) but increasing sensitivity is always accompanied by a decrease in specificity. Another limitation was the lack of advanced segmentation methods to perform volumetric analysis, because 3D acquisition with high-resolution imaging was not available at all centres participating in this clinical trial.

In conclusion, early low-dose hydrocortisone given early after birth in extremely preterm infants was associated with no significant changes in WM brain damage assessed by MRI at TEA. A slight increase in the occurrence of overall brain abnormalities was found in analysis of the cumulative distribution of the global

Kidokoro score, but analyses considering potential confounding variables did not confirm this association. The frequency of other brain abnormalities within the cortical and deep GM and cerebellum was no different after hydrocortisone exposure. This study also shows that BPD at 36 weeks PMA appears to be highly predictive of abnormal MRI at TEA in extremely preterm infants, consistent with neurodevelopmental outcomes.

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Contributors MA and BT carried out data analyses, and revised the manuscript. AT, AB and DM designed the statistical analytical plan, carried out the analyses and participated in their interpretation. CA co-ordinated and supervised the statistical methods and analyses, and revised the manuscript. VB participated in the interpretation of the analyses and revised the manuscript. OB conceived the study, participated in the interpretation of the analyses and wrote the manuscript. All authors have approved the final manuscript as submitted and agree to be held accountable for all aspects of the work.

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ORCID iD

Olivier Baud http://orcid.org/0000-0001-5021-0522

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