JAMA (2017)

Association Between Early Low-Dose Hydrocortisone Therapy in Extremely Preterm Neonates and Neurodevelopmental Outcomes at 2 Years of Age

OLIVIER BAUD, MD, PHD; CLÉMENCE TROUSSON, MSC; VALÉRIE BIRAN, MD, PHD; EMILIE LEROY, MSC; DAMIR MOHAMED, MSC; CORINNE ALBERTI, MD, PHD; FOR THE PREMILOC TRIAL GROUP

Presenter : THJ

Date: 2017/06/20

Background

- Postnatal dexamethasone therapy for preterm birth:
  - Pros: decreasing the duration of mechanical ventilation and the severity of broncho-pulmonary dysplasia
  - Cons: associated with cerebral palsy and other adverse neurodevelopmental events.
- The incidence and severity of bronchopulmonary dysplasia increased con-currently with the decreased use of postnatal dexamethasone, and it remains a major public health challenge.
- A strategy was proposed using low-dose hydrocortisone to maintain clinically relevant respiratory benefits while avoiding potential adverse effects on the developing brain.

The objective

- The PREMILOC trial found that hydrocortisone therapy resulted in a significant increase of 9 percentage points (60% vs 51%) in the rate of bronchopulmonary dysplasia–free survival at 36 weeks of postmenstrual age.
- **To assess whether early hydrocortisone therapy is associated with neuro developmental impairment at 2 years of age in children enrolled in the PREMILOC trial.**

Population and Study Protocol

- Surviving infants enrolled in the PREMILOC trial conducted in France between 2008 and 2014 were eligible for the 2-year follow-up.
- PREMILOC trial: double-blind, multicenter, randomized, placebo-controlled trial.
- Infants born between 24 0/7 weeks and 27 6/7 weeks of gestation
- Before 24 hours of postnatal age assigned either placebo or low-dose hydro-cortisone (100 mg for injection ; 0.5 mg/kg twice per day for 7 days, followed by 0.5 mg/kg per day for 3 days).
- 1:1 randomization was stratified by gestational age group (24-25 /26-27)

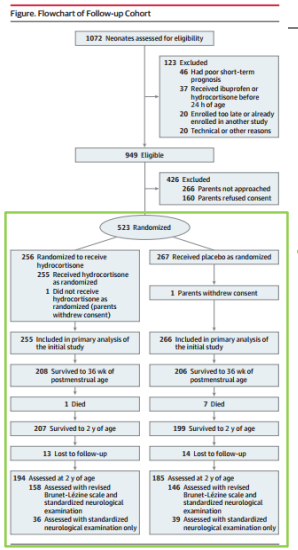
Follow-up Study Procedures and Outcomes

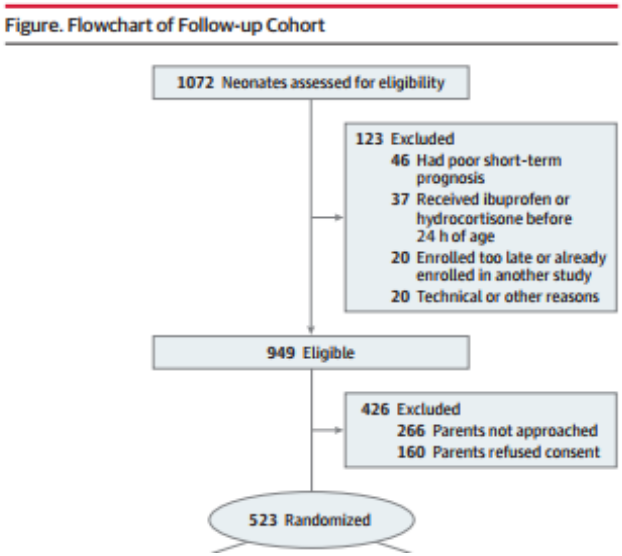
- The primary outcome of the trial, bronchopulmonary dysplasia–free survival at 36 weeks of postmenstrual age, has been reported.
- Secondary end points, neurocognitive development at 18 to 24 months was selected for this analysis.
- Follow-up evaluation at 2 Years of Age:
  - Medical history
  - Anthropometric measures
  - Respiratory status
  - **Standardized neurological examination based on specific definitions of disabilities**
  - **Quantitative neuro-developmental assessment using the revised Brunet-Lezine (RBL) scale.**

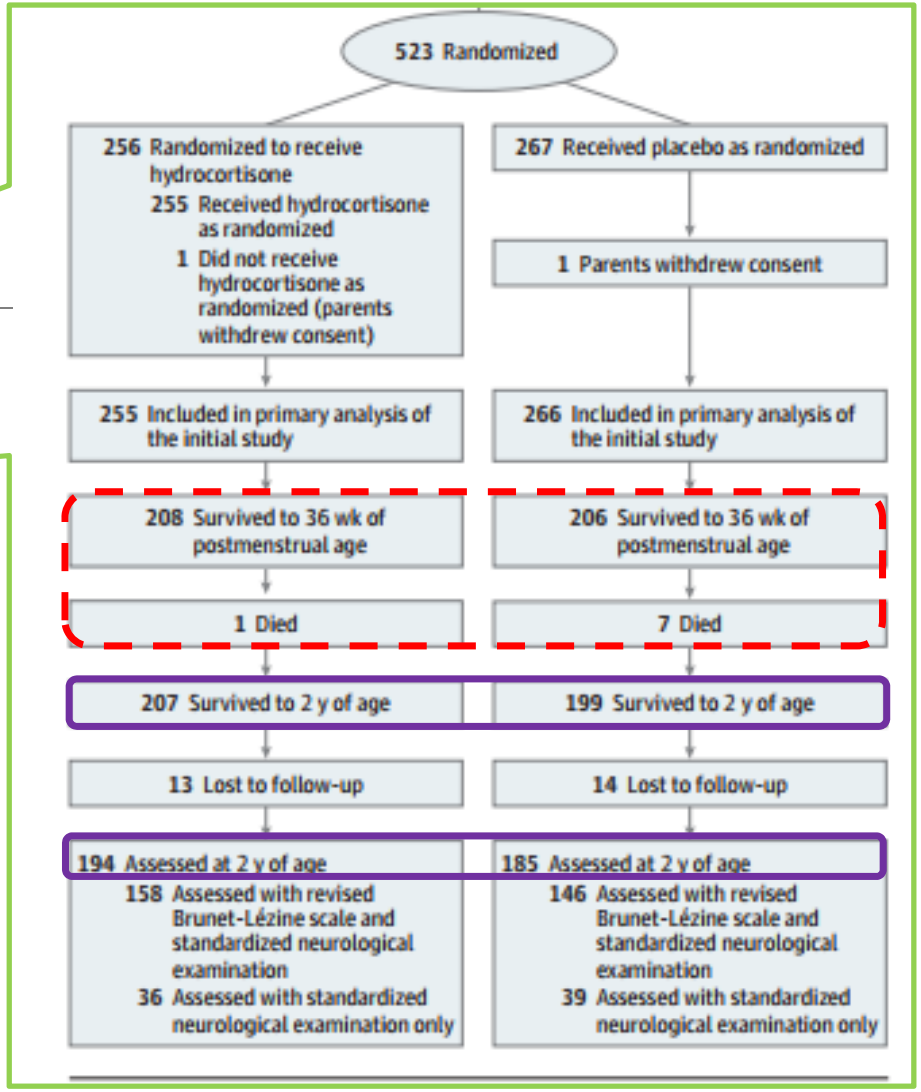
Statistical Analysis

- means and 95% CIs for continuous variables and numbers and percentages for categorical variables
- Comparisons between treatment groups were made using the ***t* test** for quantitative variables and the **χ^2 test** or **Cochran-Armitage trend test** for categorical variables.
- A **log binomial regression model** was built to study the relationship between the exploratory outcome of survival free of bronchopulmonary dysplasia or neurodevelopmental impairment and treatment that was adjusted for gestational age group.
- Results are provided as **risk difference** and **relative risk**.

Follow-up Cohort







Result:

Table 1. Population Characteristics of Patients Assessed at 2 Years of Age and Their Mothers

	No. (%)[a]		Between-Group Difference, % (95% CI)	*P* Value
	Hydrocortisone (n = 194)	Placebo (n = 185)		
Baseline Maternal Characteristics at Randomization				
Maternal racial or ethnic group[b]				
Caucasian	84 (43)	84 (45)		
Black	75 (39)	62 (34)		
Asian	7 (4)	10 (5)		
Other[c]	24 (12)	25 (14)		
Maternal employment status[d]				
None or unemployed	120 (62)	108 (58)		
Vendor or salesperson	6 (3)	2 (1)		
Unskilled occupation	6 (3)	4 (2)		
Office and administrative support occupation	45 (23)	54 (29)		
Consultant or intellectual occupation	12 (6)	9 (5)		
Unknown	5 (3)	8 (4)		
Multiple pregnancy[e]	63 (32)	64 (35)		
Histological chorioamnionitis, No./total (%)	88/180 (49)	91/172 (53)		
Gestational diabetes	6 (3)	12 (6)		
Gestational hypertension	26 (13)	12 (6)		
Antenatal steroid use	187 (96)	177 (96)		
Prenatal antibiotic use	138 (71)	132 (71)		
Prolonged rupture of membranes >24 h	59 (30)	60 (32)		
Tocolysis	128 (66)	129 (70)		

	No. (%)[a]		Between-Group Difference, % (95% CI)	*P* Value
	Hydrocortisone (n = 194)	Placebo (n = 185)		
Infant Birth Characteristics				
Vaginal delivery	101 (52)	97 (52)		
Gestational age at birth, mean (SD), wk	26.6 (0.9)	26.5 (0.9)		
Birth weight, mean (SD), g	882 (149)	888 (156)		
Male sex	99 (51)	106 (57)		
Clinical Status of Infants at 36 wk of Postmenstrual Age				
Ventilatory support				
Invasive or noninvasive ventilation	35 (18)	43 (23)	−5 (−13 to 29)	
Supplemental oxygen	30 (15)	37 (20)	−5 (−12 to 32)	.07[f]
Room air spontaneous ventilation	129 (66)	105 (57)	9 (0 to 19)	
Bronchopulmonary dysplasia	51 (26)	64 (35)	−9 (−18 to 1)	.08
Surgery for patent ductus arteriosus	31 (16)	44 (24)	−8 (−15 to 2)	.06
Necrotizing enterocolitis	14 (7)	11 (6)	1 (−3 to 6)	.62
Gastrointestinal perforation	5 (3)	4 (2)	1 (−3 to 4)	.25[g]
Severe nosocomial sepsis	57 (29)	42 (23)	6 (−2 to 16)	.14
Severe brain injury	13 (7)	19 (10)	−3 (−9 to 2)	.21

Result:

Table 2. Anthropometric Characteristics and Respiratory Outcomes in Children Successfully Followed up at 2 Years of Age

	Hydrocortisone	Placebo	Between-Group Difference, % (95% CI)[a]	*P* Value
Anthropometric Characteristics				
Corrected age at follow-up, median (IQR), mo	22 (21 to 23)	22 (21 to 23)	0 (−0.32 to 0.55)[b]	.61
Weight, mean (SD)[c]	−0.91 (1.30)	−0.78 (1.24)	−0.13 (−0.40 to 0.14)[b]	.34
No. of children	176	176		
Length, mean (SD)[c]	−0.65 (1.40)	−0.70 (1.11)	0.05 (−0.22 to 0.31)[b]	.75
No. of children	171	172		
Head circumference, mean (SD)[c]	−0.67 (1.55)	−0.79 (1.44)	0.12 (−0.45 to 0.21)[b]	.47
No. of children	163	160		
Respiratory Outcomes, No./Total (%)				
Wheezing	27/170 (16)	31/169 (18)	2 (−11 to 6)	.55
Asthma	45/177 (25)	44/174 (25)	0 (−9 to 9)	.98
Nocturnal cough	19/164 (12)	31/164 (19)	−7 (−15 to 0)	.06
Visit to lung specialist	27/173 (16)	20/170 (12)	4 (−3 to 11)	.30
Supplemental oxygen	3/194 (2)	1/185 (1)	1 (−1 to 3)	.33
Treatment for respiratory problems	85/183 (46)	86/178 (48)	−2 (−12 to 8)	.72

Abbreviation: IQR, interquartile range.

[a] Unless otherwise indicated.

[b] Expressed as the mean difference (95% CI).

[c] Expressed as a *z* score, which is the deviation from the mean value for the sex- and age-specific reference population, divided by the SD for the reference population. The *z* scores were generated using the French AUDIPOG (Association des Utilisateurs de Dossiers Informatisés en Pédiatrie, Obstétrique et Gynécologie) growth charts.

Result:

Table 3. Neurodevelopmental Outcomes at 2 Years of Age

	No. (%)[a]		Between-Group Difference, % (95% CI)	*P* Value
	Hydrocortisone (n = 194)	Placebo (n = 185)		
Primary Outcome				
Degree of neurodevelopmental impairment[b]				
None	141 (73)	130 (70)	3 (−7 to 12)	.33[c]
Mild	39 (20)	34 (18)	2 (−6 to 10)	
Moderate to severe	14 (7)	21 (11)	−4 (−10 to 2)	
Secondary Outcomes				
Disability assessment via standardized neurological examination[d]				
None	80 (41)	77 (42)	−1 (−10 to 10)	.87[c]
Mild	68 (35)	61 (33)	2 (−8 to 12)	
Moderate to severe	46 (24)	47 (25)	−1 (−10 to 7)	
Other major neurodevelopmental outcomes				
Cerebral palsy	12 (6)	10 (5)	1 (−3 to 6)	.76
Hemiplegia	1 (<1)	1 (<1)		
Seizures	2 (1)	2 (1)		>.99[e]
Ventriculoperitoneal shunting	2 (1)	2 (1)		>.99[e]
Auditory impairment, No./total (%)	3/190 (2)	6/179 (3)	1 (−5 to 1)	.33[e]
Visual impairment, No./total (%)	26/189 (14)	27/179 (15)	1 (−9 to 6)	.72
Revised Brunet-Lézine scale[f]				
No. of patients	158	146		
Global developmental quotient score, mean (95% CI)	91.7 (89.7 to 93.8)	91.4 (89.1 to 93.7)	0.3 (−2.7 to 3.4)[g]	.83
Global developmental quotient score categories, No./total (%)				
≥85 (no disability)	121 (77)	110 (75)	2 (−8 to 11)	.51[c]
70-84 (mild disability)	30 (19)	25 (17)	2 (−7 to 11)	
<70 (moderate to severe disability)	7 (4)	11 (8)	−3 (−9 to 2)	
Gross motor function developmental quotient score, mean (95% CI)	99.7 (96.8 to 102.6)	99.4 (96.1 to 102.7)	0.3 (−4.1 to 4.6)[g]	.90
Visuospatial coordination developmental quotient score, mean (95% CI)	90.0 (87.6 to 92.4)	90.1 (87.7 to 92.5)	−0.1 (−3.5 to 3.3)[g]	.95
Language developmental quotient score, mean (95% CI)	85.6 (83.1 to 88.1)	85.0 (82.1 to 87.8)	0.6 (−3.1 to 4.4)[g]	.75
Sociability developmental quotient score, mean (95% CI)	97.5 (94.8 to 100.2)	96.4 (93.3 to 99.5)	1.1 (−3.0 to 5.2)[g]	.59

Result

- Hydrocortisone was associated with **survival free** of neonatal bronchopulmonary dysplasia or neurodevelopmental impairment at **22 months** compared with placebo (46.1% vs 36.2%, respectively; risk difference, 9.4 [95% CI, 1.2-17.6] relative risk, 1.27[95%CI,1.03-1.57]; P=.03).
- After adjustment for gestational age group, the number of patients needed to treat to gain 1 patient surviving free of bronchopulmonary dysplasia and neurodevelopmental impairment was 11 (95% CI,6-83)

Strength & Limitation

- Strength:
  - Small number of children lost to follow-up (7%).
  - The population included in the present trial was comparable with larger national and multinational cohorts.
- Limitation:
  - Lack of multiple comparisons adjustment for exploratory outcomes.
  - The analysis did not account for death as a competing risk because neurodevelopmental impairment could only be studied in survivors.

Conclusion

- In this exploratory analysis of secondary outcomes of a randomized clinical trial of extremely preterm infants, **early low dose hydrocortisone was NOT associated with a statistically significant difference in neurodevelopment at 2 years of age.** Further randomized studies are needed to provide definitive assessment of the neurodevelopmental safety of hydrocortisone in extremely preterm infants.

THE END… THANK YOU!