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Early low-dose hydrocortisone: is the neurodevelopment affected?

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Abstract

Type of investigation—Prognosis; exploratory secondary analysis of an interventional randomized controlled trial.

Question—In extremely preterm infant (<28 weeks), is early low-dose hydrocortisone compared to placebo associated with neurodevelopmental impairment at 2 years of age?

Methods

Patients: Surviving infants enrolled in the PREMILOC trial conducted in France between 2008 and 2014.

Intervention: Double-blind, multicenter, randomized, placebo-controlled trial of infants born between 24 0/7 weeks and 27 6/7 weeks of gestation and before 24 h of postnatal age, assigned to receive either placebo or low-dose hydrocortisone (0.5 mg/kg twice per day for 7 days, followed by 0.5 mg/kg per day for 3 days).

Main results—For the pre-specified exploratory outcome, the distribution of patients without neurodevelopmental impairment (73% in the hydrocortisone group vs. 70% in the placebo group), with mild neurodevelopmental impairment (20% in the hydrocortisone group vs. 18% in the placebo group), or with moderate to severe neurodevelopmental impairment (7% in the hydrocortisone group vs. 11% in the placebo group) was not found to be statistically significantly different between the two groups ($p = 0.33$). Qualitative assessment of patients using standardized neurological examination also was not statistically significantly different between groups ($p = 0.87$).

Study conclusion—In this follow-up study of premature infants who were randomly assigned at birth to receive low-dose hydrocortisone or placebo for 10 days, hydrocortisone treatment was not associated with any adverse effects on neurodevelopmental outcome at 22 months of corrected age.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Commentary

There is a clear rationale for the use of postnatal steroids for bronchopulmonary dysplasia (BPD) prophylaxis or treatment. Steroids are potent anti-inflammatory agents. A large proportion of premature infants are exposed prenatally to chorioamnionitis and have evidence of early lung inflammation [1]. This inflammatory process is further aggravated postnatally by exposure to oxidative stress and mechanical ventilation. In addition, fetal cortisol synthesis is immature such that the fetus makes minimal cortisol; therefore, many very low birthweight infants will have low blood cortisol values and may be functionally adrenally insufficient [2]. Last, animal studies demonstrate that postnatal steroids can have dose-dependent and variable effects on the developing lung, from inducing alveolarization arrest to attenuation of hyperoxia-induced pulmonary vascular remodeling [3, 4].

Historically, follow-up studies have raised concerns that postnatal systemic corticosteroid therapy contributes to neurodevelopmental impairment, in particular cerebral palsy (CP) [5].

In a review of 20 randomized controlled trials, the risk of CP was greater in infants who received corticosteroid therapy than control infants (15.2 vs. 10.3%) [6]. Doyle et al. [7, 8] addresses long-term outcome of early (<8 days of age) and late (>7 days of age) steroids administration in two meta-analyses. Long-term data showed early dexamethasone treatment was associated with increased risk of an abnormal neurologic examination, developmental delay, and CP. In contrast, a subgroup analysis showed no significant effect of early hydrocortisone treatment on these neurodevelopmental outcomes. The dexamethasone studies utilized a mean cumulative dose of 3 mg/kg of dexamethasone or the equivalent of 76 mg/kg of hydrocortisone. This is compared to the PREMILOC cumulative dose of 8.5 mg/kg. On the other hand, while high-dose dexamethasone is associated with both short-term and long-term adverse outcomes, it remains uncertain whether low-dose early corticosteroid therapy is effective or safe in preterm infants at risk for or with established BPD. Late administration of corticosteroids, however, was not associated with differences in rate of CP, major neurosensory disabilities, combined outcome of death and CP, and combined outcome of death and major neurosensory disabilities when compared to placebo.

There are additional concerns about effects of postnatal steroids on brain volumes of former premature infants. Cheong et al. [6] studied 148 extremely preterm participants at 18 years of age. Thirty-seven percent of studied patients received dexamethasone (cumulative mean dose of 7.7 mg/kg) and had smaller total brain and white matter tissue volumes on magnetic resonance imaging, effects that became more pronounced with increasing dose of postnatal dexamethasone [6]. These data resulted in the recommendation by the American Academy of Pediatrics and the Canadian Pediatrics Association to avoid routine use of postnatal corticosteroids for prevention or treatment of BPD [9]. Practice changed from a more ubiquitous use to one restrained to the most difficult cases.

In the PREMILOC study, infants were exposed to hydrocortisone for a total of 10 days with doses comparable to baseline cortisol levels. The primary outcome of the trial was survival without BPD, which was significantly increased by the intervention. This was as a combined

result of fewer deaths and less BPD, but neither mortality nor BPD individually was statistically different between the two groups.

In the current report, there was no difference in the developmental outcome between the two groups but, in contrast to the improved primary outcome of survival without BPD, clinically important respiratory outcomes up to 2 years of age were not affected, and there was no effect on growth among the survivors. Based on these results, there is no negative long-term neurodevelopmental impact, but no long-term respiratory improvement either. It is also important to consider that in the initial data from this trial there was also a non-significant but higher rate of necrotizing enterocolitis and severe retinopathy of prematurity, with a statistically significant increase of late onset sepsis in the subgroup of infants born at 24–25 weeks gestation (40 vs. 23%).

There are several issues in trying to understand the effect of steroid use in the neonatal population. Postnatal corticosteroids are often given to the sickest premature infants who are at the highest risk for development of BPD. These patients often have multiple comorbidities and are at risk for neurodevelopmental delay independent of corticosteroid use. RCTs are important to prevent attributing outcomes to a treatment when they could be due to the multiple comorbidities and complications experienced by this population of infants. In addition, infants frequently receive corticosteroids for indications other than BPD, for example, hypotension or airway management after extubation. The goal remains to find the right dose of the right steroid given at the right time by the right route in order to best improve the outcomes of our extremely low birthweight infants.

EBM lesson: biases in secondary analysis

In this study, Baud et al. [10] utilizes secondary analysis to investigate the neurodevelopmental outcome after early low-dose hydrocortisone exposure. Secondary analysis is meant to study additional events of interest, which the primary study is not specifically powered to assess. Therefore, this study is a post hoc analysis. Post hoc analyses need to be viewed with caution because end points that favor treatment group can be chosen.

One of the main biases when performing a secondary analysis on an RCT is selection bias. Selection bias can occur when the number of subjects at the start of the study is different (lower) at the end, leading to differences in the cohort composition of those in the study vs. those lost to follow-up (or unobserved). In this study, this is avoided because 93% of the 406 surviving infants included in the primary study were seen at 22 months corrected age.

An assessment of unmeasured confounders is particularly relevant to studies examining outcomes that remain temporally distant from the exposure. In the case of 2-year assessment of neurodevelopmental outcomes in relation to exposures to hydrocortisone, a number of confounders may have played a role in shaping the risks of neurodevelopmental deficits. The commonly applied methods to estimate the impact of, and correct for, unmeasured confounding include bias modeling and sensitivity analyses. The final categorical determination of neurodevelopmental impairment was based on the presence of either (1) abnormal RBL score (70–84 mild, <70 moderate/severe), abnormal exam, or CP. Therefore,

children may have been categorized based on the presence of one or all of these characteristics. The authors do not discuss how concordant these characteristics were, and it is possible that some infants had conflicting discordant categories based on RBL vs. neurologic exam. Therefore, a sensitivity analysis might compare final NDI status based on RBL score alone, as well as final NDI status based on exam alone. This would allow for a cleaner analysis.

A sample size calculation in an RCT is key to planning the statistical analysis. However, secondary analyses of RCTs are limited to the sample size in the original RCT. The authors acknowledge that the study power and sample size were primarily calculated for the outcome of survival without BPD at 36 weeks of post menstrual age. Despite a lack of power analysis for the secondary outcome the authors interpret the results with a 95% confidence interval and a standard measure of clinical relevance, lending credibility to their study.

Assessing long-term neurological outcomes involves significant costs and logistics. Having to examine the changes in neurodevelopmental outcome after hydrocortisone exposure as a primary hypothesis would require a higher number of patients. The future proposed studies, to be done at 5 to 7 years of age, may provide further information, although likely at risk of having an even smaller sample size. In this case, secondary analysis prompts more questions for future research.

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