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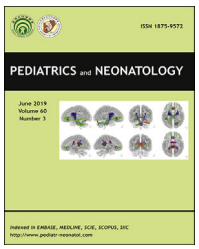

Short Communication

Effect of postnatal hydrocortisone on 18-month neurodevelopmental outcomes in very-low-birth-weight infants

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1. Introduction

Potential neurodevelopmental impairments following postnatal corticosteroid therapy in preterm infants are a concern. Although hydrocortisone has been more commonly used than dexamethasone, its long-term neurodevelopmental impact remains debatable.[1–3] In addition, hydrocortisone exposure for longer than 7 days has been associated with poor performance in fine motor skills during the first year of life.[4] Moreover, the safety range of dose and the duration of hydrocortisone still remain undetermined; therefore, we investigated the effect of cumulative dose and treatment duration of hydrocortisone on neurodevelopmental outcomes.

2. Methods

This retrospective study included very-low-birth-weight (VLBW) infants who were born between 2008 and 2015 and received hydrocortisone treatment at the neonatal intensive care units of Toyama University Hospital and Toyama Prefectural Central Hospital. The medical charts of the VLBW infants were reviewed to assess the dose and treatment duration of hydrocortisone. The neurodevelopmental outcomes among the infants were analyzed at a corrected age of 18 months using the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III). The relationship between Bayley-III scores and the cumulative doses and treatment duration of hydrocortisone was examined. Our indication for hydrocortisone therapy was refractory hypotension regardless of volume boluses and inotropic therapy or respiratory deterioration that required fraction of inspired oxygen (FiO_2) >0.40 for intubated preterm infants. Hydrocortisone was generally initiated at 3 mg/kg per day for 3 days, and tapering off the dose was attempted for 7 days; however, there was no precise protocol for tapering off the dose. Therefore, all the neonatologists administered hydrocortisone according to their own discretion.

This study was approved by the Research Ethics Committee of the University of Toyama (No. 27-135). Data were summarized as mean ± standard deviation. The correlation

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between Bayley-III scores and the cumulative dose or duration of hydrocortisone treatment was assessed using Spearman's rank correlation coefficient. A p value < 0.05 was considered to be statistically significant. All statistical analyses were performed using JMP version 12.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 32 infants who received hydrocortisone treatment underwent assessment of neurodevelopmental outcomes at a corrected gestational age of 18 months. Their mean gestational age was 25.3 ± 2.1 weeks, mean birth weight was 788.6 ± 215.5 g, and the rate of bronchopulmonary dysplasia with oxygen dependency at 36 weeks of post-menstrual age was 91%. The indication for hydrocortisone therapy was respiratory exacerbation in 29 infants (91%) and hypotension in 3 infants (9%). The mean age at the start of hydrocortisone therapy was 15.6 ± 10.5 days, and the duration of therapy was 18.2 ± 16.5 days. The mean cumulative dose of hydrocortisone was 29.2 ± 21.2 mg/kg.

The mean Bayley-III scores (cognitive, language, and motor skills) were 87.7 ± 16.0, 83.2 ± 17.8, and 88.4 ± 12.5, respectively. The correlations between the Bayley-III scores and the cumulative dosage and duration of hydrocortisone are shown in Fig. 1. After adjusting for gestational age, no correlation was observed between Bayley-III scores and the cumulative dose and duration of hydrocortisone.

4. Discussion

Although our study demonstrated no correlation between Bayley-III scores and the cumulative dose and duration of hydrocortisone, Patra et al. retrospectively reported that hydrocortisone exposure for more than 7 days was associated with poor performance in fine motor skills during the first year of life.[4] These conflicting outcomes may be influenced by the early start date and the increased cumulative duration of hydrocortisone treatment in their study. In the present study, the mean start day of hydrocortisone therapy was day 15.6; however, hydrocortisone treatment was initiated for approximately 50% of the patients by day 14 in the study of Patra et al.[4] Moreover, the mean cumulative duration of hydrocortisone treatment (49 days) in that study was much longer than that in our study (18 days). Renault et al. reported that the effect of hydrocortisone treatment on neurodevelopmental outcomes may depend on the patient's age at the initiation of therapy.[5] In addition, another study demonstrated that the expression of glucocorticoid receptors was downregulated by exogenous glucocorticoids, which significantly differed according to age.[6] These results suggest that preterm infants have a critical neurodevelopmental

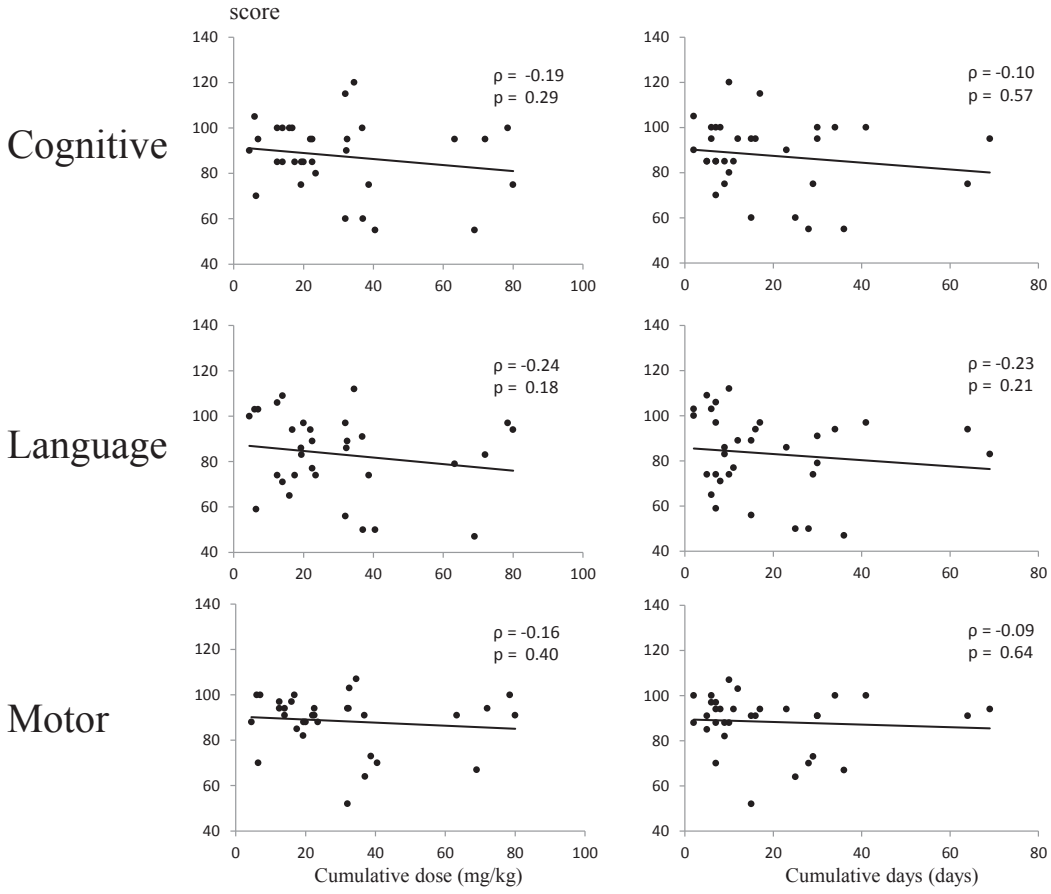

Figure 1 The relationship between Bayley-III scores (cognitive, language, and motor skills) and the cumulative doses and duration of hydrocortisone.

period that is vulnerable to glucocorticoids. Therefore, additional research is required to determine the appropriate start date of the duration and the cumulative dose of hydrocortisone treatment. The present study has several limitations. First, this was a retrospective study without a clearly defined protocol for hydrocortisone administration. Furthermore, the sample size was too small to be compared with other large reports or meta-analyses; however, this study provides important information regarding hydrocortisone and its impact on neurodevelopment in preterm infants. Additional multicenter, randomized, controlled studies are required to determine the most effective and safe dose of hydrocortisone therapy for preterm infants.

Conflicts of interest

All contributing authors declare no conflicts of interest. This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2018.10.005.