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Total Hydrocortisone Dosage in the Neonatal Period May Be Related to Low Developmental Quotient in Extremely Low Birth Weight Infants: A Retrospective Cohort Study

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Keywords
Hydrocortisone · Neurodevelopment · Extremely low birth weight infants · Steroid

Abstract

Introduction: The effects of hydrocortisone (HDC) administration to extremely low birth weight (ELBW) infants on later development remain unclear. This study examined the association between HDC dosage during neonatal period and neurodevelopmental outcomes in ELBW infants. ***Methods:*** This study was a retrospective cohort study conducted in eight centers in Japan. The subjects of this study were ELBW infants born between April 2015 and March 2017. The association between postnatal total HDC dosage up to 36 weeks postmenstrual age and the developmental quotient (DQ) at 3 years of age was examined. Multiple linear regression evaluated the association, adjusting for weeks of gestation, birth weight, and the presence of bronchopulmonary dysplasia, late-onset circulatory collapse, intracranial hemorrhage, necrotizing enterocolitis, and sepsis. ***Results:*** This study included 218 ELBW infants, of whom 144 underwent a developmental test at 3 years of age. Simple linear regression analysis revealed a significant association between total HDC dosage and DQ at 3 years of age (coefficients: −2.65, 95% CI: −3.73, −1.57). Multiple linear regression analysis adjusted for the presence of bronchopulmonary dysplasia and late-onset circulatory collapse also revealed a significant association between total HDC dosage and DQ at 3 years of age (coefficients: −2.66, 95% CI: −3.89, −1.42). ***Conclusion:*** Higher total HDC dosage up to 36 weeks postmenstrual age in ELBW infants was associated with impaired neurodevelopmental outcomes. Although HDC is often needed in the treatment of ELBW infants,

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clinicians should be aware that an increased dose of HDC may be associated with impaired neurodevelopmental outcomes.

Introduction

Extremely low birth weight (ELBW) infants require intensive care including various medication administrations. Postnatal steroids have mainly been used in treating hypotension, including late-onset circulatory collapse (LCC) [1], and in the prevention/treatment of bronchopulmonary dysplasia (BPD) [2]. Dexamethasone became widely used in the 1990s–2000s after reports of short-term respiratory benefits [3]. However, its use has declined due to the emergence of side effects, in particular, cognitive impairment and neurodevelopmental disorders such as cerebral palsy [4]. Even low doses of dexamethasone could lead to poor neurodevelopment in both animal and clinical studies [5, 6].

Hydrocortisone (HDC) was considered an alternative to dexamethasone as a glucocorticoid treatment for neonates [7, 8]. In newborn rats, dexamethasone treatment had a detrimental effect on neurodevelopment, whereas HDC had no harmful effect on neurodevelopment [8, 9]. A recent randomized controlled trial (RCT) of HDC involving ELBW infants revealed no evidence of adverse neurodevelopmental effects at the age of 2 years [10–12]. These studies have shown that developmental outcomes are not worse in groups that used HDC to prevent BPD, but neonatal steroid administration for other reasons has not been fully evaluated.

This study examined the association between HDC dosage in neonatal intensive care unit (NICU) and developmental outcomes in ELBW infants because no studies have examined HDC dosage in detail and compared its association with developmental outcomes. We hypothesized that the total HDC dosage for ELBW infants is correlated with impaired neurodevelopment.

Materials and Methods

Study Design and Participants

This retrospective multicenter observational study included ELBW infants (born birth weight of <1,000 g) born from April 1, 2015, to March 31, 2017, at Nagoya University Hospital, Anjo Kosei Hospital, Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Konan Kosei Hospital, Ogaki Municipal Hospital, Okazaki City Hospital, Tosei General Hospital, and Toyota Memorial Hospital. The participating centers did not administer prophylactic steroids uniformly to ELBW infants. Steroids are used when the neonatologist determines that they are necessary for treatment, such as to improve respiratory status requiring sustained fraction of inspiratory oxygen (FiO_2) >0.4 or to improve hypotension or circulatory failure due to LCC or infection. Maternal and neonatal data from birth until home discharge, transfer, or death were retrospectively collected.

Morbidities included necrotizing enterocolitis, sepsis, intracranial hemorrhage (grade 3 or 4) [13], cystic periventricular leukomalacia, BPD, and LCC. BPD was defined as the use of supplemental oxygen, positive-pressure ventilation, or both at 36 weeks postmenstrual age. The need for oxygenation and positive pressure ventilation was based on the judgment of the facility's treatment staff to manage the neonates keep SpO_2 above 90% and breathe without effort. LCC was defined by a doctor in charge following the diagnostic criteria suggested by the Japanese Study Group for Neonatal Endocrinology [1]: (1) LCC occurring outside the transitional period; (2) a stable period existing before the LCC onset; (3) absence of clear causes, such as sepsis, massive bleeding, or necrotizing enterocolitis before LCC onset; (4) hypotension and/or oliguria with sudden onset; and (5) hypotension and/or oliguria resistant to intravenous volume expanders and inotropes. Surviving infants were followed up and received a developmental examination at 18 months of corrected age and 3 years of age. As dexamethasone is known to affect neurodevelopment, cases where dexamethasone was used were excluded from the final analysis despite the availability of the developmental test result.

HDC Dosage

Total HDC dosage represents the total amount of intravenously or orally administered HDC from birth to 36 weeks postmenstrual age. It has been reported that HDC is absorbed orally almost as well as intravenously administration [14]. Therefore, the oral and intravenous administrations were considered equivalent in this study.

Developmental Testing

The results of the developmental examination with the Kyoto Scale of Psychological Development 2001 at 18 months of corrected age and 3 years of age were retrospectively investigated. The developmental examination at 18 months of corrected age was performed between 18 and 24 months of corrected age and 3 years of age; the developmental examination was performed between 3 and 4 years of age.

The Kyoto Scale of Psychological Development is the most standardized and validated developmental test available at all participating centers in the follow-up study of the Neonatal Research Network, Japan, whose scores were well correlated with those of Bayley III [15]. The scale is an individualized face-to-face test to assess a child's development in the following three areas: Postural-Motor (P-M; fine and gross motor functions), Cognitive-Adaptive (C-A; nonverbal reasoning or visuospatial perceptions assessed using materials), and Language-Social (L-S; interpersonal relationships, socialization, and verbal abilities). Each score for these three areas and the sum of the scores were converted for each and overall developmental ages. The developmental quotient (DQ) was calculated by dividing the developmental age by the corrected age for prematurity and then multiplying the quotient by 100. The corrected age was adjusted using the estimated date of birth instead

of the chronological date of birth at 18 months of the corrected age test. The Japanese protocol for the follow-up of infants with very low birth weight classified developmental function as "delayed" with an overall DQ of <70, "subnormal" at 70–84, and "normal" at ≥85 [16].

Outcomes

The DQ at 3 years of age was defined as the primary outcome in this study. Neonatal HDC dose was the primary exposure factor, and weeks of gestation, birth weight, and presence of BPD, LCC, intracranial hemorrhage (grade 3 or 4), necrotizing enterocolitis, and sepsis were considered confounding factors.

Statistical Analysis

We summarized patient characteristics by reporting the frequencies for categorical variables and the median, along with the interquartile range, for continuous variables. We performed a simple linear regression analysis to investigate the association between each variable and DQ at 3 years of age. To visualize the trend of DQ at 3 years of age, we conducted boxplot analysis by dividing the data into three groups according to the total HDC dosage: <10 mg, 10–20 mg, and >20 mg. Our main analysis involved using multiple linear regression to estimate the association between HDC dosage in the neonatal period and DQ at 3 years of age. The main model was constructed based on the presence or absence of BPD and LCC, which are often treated with steroid administration [1, 2]. To examine the robustness of the primary analysis results, we conducted sensitivity analyses. These analyses involved adding other perinatal confounding factors, which may be related to developmental outcomes, to the analysis in five different patterns. We calculated variance inflation factors (VIFs) to evaluate the multicollinearity among the variables of all the multiple linear regressions. To examine the impact across centers, we also constructed a linear mixed-effects model with a random effect between centers added from the main model. p values of <0.05 were evaluated as statistically significant in all analyses. All statistical analyses were performed using R (ver. 4.2.0, R Foundation for Statistical Computing, Vienna, Austria).

Results

The study population is shown in Figure 1. This study included 218 ELBW infants born at the participating hospitals. During NICU hospitalization, 20 death cases were observed. Of the remaining 198 cases, the developmental test was performed in 144 cases (73%) at 3 years of age. The developmental test at 18 months of corrected age was performed in 159 cases (80%). Table 1 shows the patient background. HDC was administered to 113 patients and dexamethasone to 5 patients. Four patients received both HDC and dexamethasone. Two cases in which data for DQ at 3 years of age and three cases in which DQ at 18 months of corrected age is available were excluded from the final analysis due to dexamethasone use.

Figure 2 demonstrates the correlation between the total HDC dosage and DQ at 3 years of age. The three groups established according to the total HDC dosage were as follows: <10 mg, 10–20 mg, and >20 mg. The median and interquartile ranges of DQ at 3 years of age were 85 (73–94), 83.5 (74.5–88.75), and 68.5 (57.5–82.75), respectively.

Table 2 shows the simple linear regression analysis results. Total HDC dosage was significantly associated with DQ at 3 years of age (coefficients: −2.65, 95% confidence interval [CI]: −3.73, −1.57; $p < 0.001$). The presence of LCC, grade 3 or higher intraventricular hemorrhage, and birth weight were significantly associated with DQ at 3 years of age. The multiple linear regression analyses are shown in Table 3. Multiple linear regression analysis adjusted for the presence of BPD and LCC revealed a significant association between total HDC dosage and DQ at 3 years of age (coefficients: −2.66, 95% CI: −3.89, −1.42; $p < 0.001$). The results of the main model showed that DQ at 3 years of age decreased by 2.66 for every 10 mg increase in total HDC dosage. Various additional confounding factors were examined (models 1–5). Significant associations between total HDC dosage and DQ at 3 years of age were coherent in all analyses. The VIFs in all the multiple linear regression models were <1.5 (online suppl. Table 3; for all online suppl. material, see https://doi.org/10.1159/000534934). Because multicollinearity among variables is defined as VIF >10, we considered that there was no multicollinearity.

Similar results were obtained for DQ at 18 months of corrected age. Simple linear regression analysis revealed a significant association between total HDC dosage and DQ at 18 months of corrected age (coefficients: −3.07, 95% CI: −4.37, −1.76; $p < 0.001$). Multiple linear regression analysis adjusted for the presence of BPD and LCC revealed a significant association between total HDC dosage and DQ at 18 months of corrected age (coefficients: −2.43, [95% CI: −4.02, −0.84]; $p = 0.003$). The total HDC dosage was significantly correlated with all Postural-Motor, Cognitive-Adaptive, and Language-Social components at 3 years of age (coefficients: −3.37, 95% CI: −5.02, −1.73, $p < 0.001$; coefficients: −2.20, 95% CI: −3.50, −0.90, $p = 0.001$; coefficients: −2.91, 95% CI: −4.38, −1.43, $p < 0.001$, respectively) with multiple linear regression analysis adjusted for the presence of BPD and LCC. (online suppl. Table 1).

The result of the linear mixed-effects model with a random effect between centers added from the main model is presented in Figure 3. Although some variations existed across centers, the effect of total HDC dosage on DQ at 3 years of age was mostly consistent between

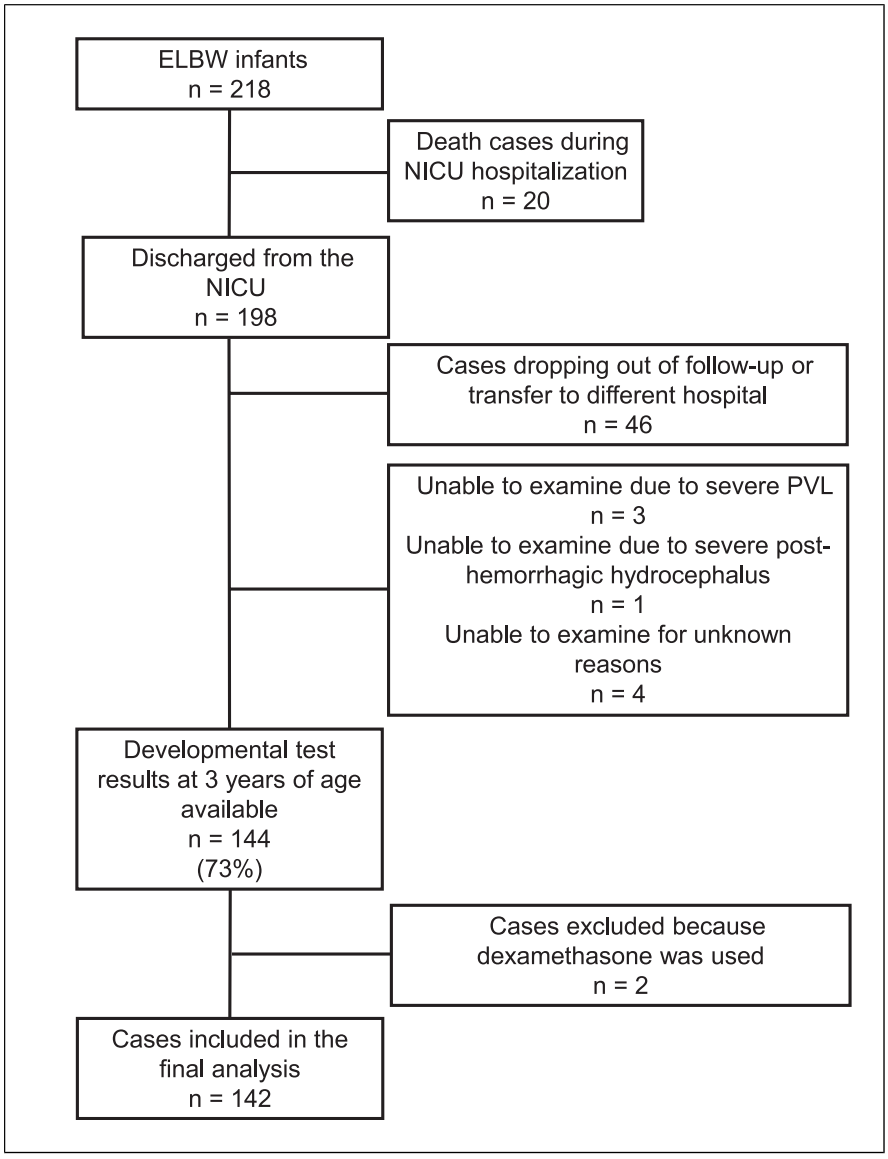

Fig. 1. Study population. NICU, neonatal intensive care unit; ELWB, extremely low birthweight; PVL, periventricular leukomalacia.

centers. The magnitude of the coefficient of the linear mixed-effects model was similar to that of the main model (online suppl. Table 2).

Discussion

This study revealed that higher total dose of HDC for ELBW infants in the neonatal period was associated with impaired developmental outcomes. Even HDC, which has often been reported to not affect the neurodevelopment of preterm infants, may be associated with impaired developmental outcomes when the total dose is increased. Several studies reported different results compared to this study. The subsequent developmental evaluation of RCTs examining whether HDC is effective in preventing BPD in ELBW and very preterm infants revealed no evidence of adverse neurodevelopmental effects at 2 years of age [10–12]. Other research revealed no reduction in brain tissue or cerebellar volumes at term-equivalent age between infants with or without HDC treatment for BPD [17]. These studies examined the presence or absence of HDC administration and the total amount of HDC used to prevent BPD, but they did not examine the total amount of HDC administered in the neonatal period, which may have led to different results from those in this study.

The mechanism by which perinatal glucocorticoid exposure causes long-term effects is not completely

Table 1. The perinatal demographic characteristics

	Overall (n = 218)	Survival cases (n = 198)	DQ at 18 months of corrected age is available (n = 159)	DQ at 3 years of age is available (n = 144)
Females/males	107/111	97/101	79/80	67/77
Gestational age, weeks[a]	26 (25–27)	26 (25–27)	27 (25–28)	26 (25–27)
Birth weight, g[a]	757 (592–908)	778 (617–919)	794 (622–912.5)	781.5 (630–912)
Apgar score (5 min)[a]	6 (4–8)	6 (4–8)	6 (4.5–8)	6 (5–8)
Singleton, *n* (%)	167 (77)	149 (75)	116 (73)	106 (74)
Antenatal steroid, *n* (%)	142 (66)	133 (68)	109 (69)	100 (70)
Pre-labor rupture of membranes, *n* (%)	69 (32)	62 (32)	48 (31)	47 (33)
Cesarean delivery, *n* (%)	180 (85)	169 (86)	134 (84)	109 (83)
HDC use, *n* (%)	113 (52)	109 (55)	82 (52)	76 (53)
HDC dosage, mg[a]	0.75 (0–11.8)	1 (0–11.8)	0.75 (0–9.3)	1 (0–9.6)
Dexamethasone use, *n* (%)	5 (2)	4 (2)	3 (2)	2 (1)
IVH (≥ grade 3), *n* (%)	18 (9)	13 (7)	11 (7)	10 (7)
PVL, *n* (%)	9 (4)	9 (5)	3 (2)	2 (1)
BPD, *n* (%)	128 (64)	122 (64)	95 (62)	86 (61)
NEC, *n* (%)	7 (3)	4 (2)	3 (2)	3 (2)
Sepsis, *n* (%)	17 (8)	13 (7)	8 (5)	5 (3)
LCC, *n* (%)	57 (28)	55 (28)	40 (25)	37 (26)

HDC, hydrocortisone; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; LCC, late-onset circulatory collapse. [a]Median (IQR).

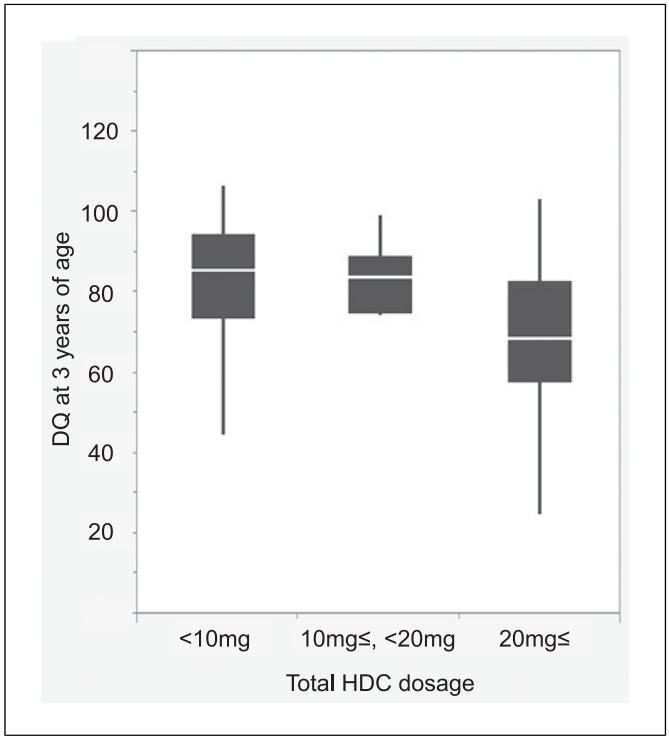

Fig. 2. Relationship between total HDC dosage and DQ at 3 years of age. The median and interquartile ranges of DQ at 3 years of age were 85 (73–94), 83.5 (74.5–88.75), and 68.5 (57.5–82.75), respectively. HDC, hydrocortisone; DQ, developmental quotient.

understood, but previous studies in rats demonstrated that dexamethasone and HDC can transiently suppress neuronal proliferation and astrogliosis [18, 19]. Exogenous glucocorticoids are associated with neuropsychiatric side effects, including not only potentially severe mood disturbances, such as depression and mania, but also cognitive impairment, such as concentration and memory problems [20]. Chronic glucocorticoid use in the adult domain has been involved in changes in the brain nervous system, such as white matter integrity, and may contribute to impaired executive cognitive function and neuropsychiatric side effects [21, 22]. Brain function may be impaired as a side effect of glucocorticoid administration even in the neonatal period, which may account for the results of this study.

This study confirmed that the random effect by centers and the VIFs for each variable were sufficiently small to be statistically acceptable. The strength of this study is that it evaluated the center effect and multicollinearity among the variables and confirmed that they do not affect the results. In the linear mixed-effects model, the intercept was variable, suggesting inter-center differences that the DQ at 3 years of age vary across centers. Conversely, the magnitude of the association between HDC and DQ at 3 years of age was nearly consistent across centers. Coefficient of the

Table 2. Simple linear regression analysis of each variable on DQ at 3 years of age

Variable	DQ at 3 years of age (coefficients [95% CI] (*p* value))
Total hydrocortisone dosage per 10 mg	−2.65 [−3.73, −1.57] (<0.001)
BPD, yes	0.52 [−5.37, 6.42] (0.861)
LCC, yes	−9.34 [−15.67, −3.02] (0.004)
IVH (≥ grade 3), yes	−12.94 [−23.79, −2.08] (0.020)
NEC, yes	−10.14 [−29.16, 8.88] (0.294)
Sepsis, yes	−14.16 [−29.33, 1.01] (0.067)
Gestational age per 1 week	0.96 [−0.36, 2.28] (0.151)
Birth weight per 100 g	1.99 [0.39, 3.59] (0.015)

DQ, developmental quotient; BPD, bronchopulmonary dysplasia; LCC, late-onset circulatory collapse; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis.

Table 3. Multiple linear regression analysis of DQ at 3 years of age as the objective variable

	Adjusted coefficients [95% CI] (*p* value)					
	main model	model 1	model 2	model 3	model 4	model 5
Total hydrocortisone dosage per 10 mg	−2.66 [−3.89, −1.42] (<0.001)	−2.52 [−3.75, −1.30] (<0.001)	−2.62 [−3.84, −1.39] (<0.001)	−2.59 [−3.82, −1.36] (<0.001)	−2.66 [−3.92, −1.40] (<0.001)	−2.63 [−3.87, −1.40] (<0.001)
BPD, yes	4.16 [−1.42, 9.74] (0.143)	3.62 [−1.89, 9.13] (0.196)	4.65 [−0.81, 10.11] (0.095)	4.38 [−1.18, 9.94] (0.121)	4.15 [−1.50, 9.79] (0.148)	4.93 [−0.75, 10.61] (0.089)
LCC, yes	−3.18 [−9.90, 3.55] (0.352)	−3.73 [−10.36, 2.91] (0.268)	−2.90 [−9.52, 3.72] (0.388)	−3.07 [−9.76, 3.61] (0.365)	−3.19 [−10.08, 3.70] (0.362)	−1.28 [−8.55, 5.99] (0.728)
IVH (≥ grade 3), yes		−11.79 [−21.83, −1.75] (0.022)				
NEC, yes			−7.35 [−25.13, 10.44] (0.415)			
Sepsis, yes				−11.23 [−25.30, 2.85] (0.117)		
Gestational age per 1 week					−0.01 [−1.37, 1.34] (0.983)	
Birth weight per 100 g						1.17 [−0.56, 2.91] (0.184)
Intercept	81.38	82.55	81.58	81.54	81.77	71.43

DQ, developmental quotient; BPD, bronchopulmonary dysplasia; LCC, late-onset circulatory collapse; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis.

linear mixed-effects model was similar to that of the main model. These findings suggest the robustness of the main analysis.

This study has several limitations. First, the possibility of bias due to confounding factors cannot be ruled out due to the retrospective design, but we analyzed it statistically to minimize bias as much as possible by including confounding factors related to HDC administration and developmental prognosis in the analysis. An association was found between total HDC dosage and later DQ, even after considering confounding factors in this study. Next, the effects of steroids that were prenatally administered to the mother on the results are unclear. A study reported that antenatal exposure to betamethasone is associated with a decreased risk of cystic periventricular leukomalacia and respiratory disorders among very premature infants [23, 24]. Hence, steroids are often administered to mothers who are expected to deliver very prematurely. Examining the extent to which prenatally administered maternal steroids are

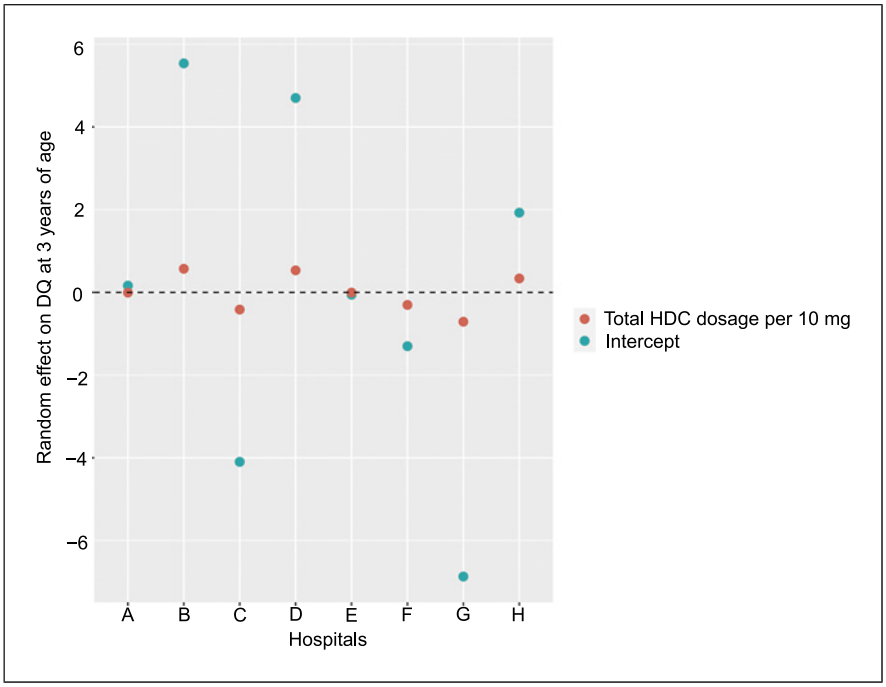

Fig. 3. Random effect of the total dose of HDC on the DQ at 3 years of age by centers. HDC, hydrocortisone; DQ, developmental quotient.

transferred to and affect the fetus is difficult, and this study was unable to include the effects of prenatally administered maternal steroids. Additionally, this study did not examine the dosage of inhaled steroids for ELBW infants. Inhaled steroids are sometimes used in ELBW infants to prevent BPD. Approximately 6% of the nominal dose reached the systemic circulation of children after nebulized steroid inhalation [25]. However, the extent of inhaled steroids migrating systemically in neonates is unclear. Another limitation is that some children are missing from follow-up, so developmental test results are unavailable. In Japan, ELBW infants are followed up until 6 years of age or older, but some cases cannot be followed up due to dropping out and/or moving.

HDC is administered to ELBW infants in various situations, including BPD prevention/treatment, hypotension treatment, and LCC. Therefore, conducting a completely randomized trial on HDC for ELBW infants is difficult, and we could only retrospectively examine as in this study.

Currently, HDC is an essential part of the respiratory and circulatory management of ELBW infants. However, the results in this study revealed that higher total HDC dosage up to 36 weeks postmenstrual age in ELBW infants was associated with low DQ. Our study's results indicate that HDC should be administered considering that increased dosage may be associated with impaired neurodevelopmental outcomes.

Conclusion

This study found that higher total HDC dosage up to 36 weeks postmenstrual age in ELBW infants was associated with impaired developmental outcomes. Although HDC is often needed in the treatment of ELBW infants, clinicians should be aware that an increased dose of HDC may be associated with impaired neurodevelopmental outcomes.

Statement of Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki and the ethical guidelines in Japan. This study protocol was reviewed and approved by the Local Ethical Committee at Nagoya University Hospital, approval number 2022-0466, approved on February 22, 2023. Since this was a clinical study using existing medical information, the Local Ethical Committee at Nagoya University Hospital has approved the request to waive documentation of informed consent, with the condition that the opportunity for parents to refuse participation in research was guaranteed by disclosing research information on the website of the collaborating institution.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization, methodology, and project administration: A.T.; investigation: A.T., E. Kataoka, N.F., E. Kato, H.Y., K.T., M.I., S.H., and T.M.; statistical analysis: K.N.; writing – original draft preparation: A.T. and K.N.; writing – review and editing: A.T., T.S., K.N., Y. Sugiyama, Y.T., and Y. Sato; supervision: Y. Sato.

Data Availability Statement

Data are available on reasonable request. The deidentified participant data and study protocol are available to investigators whose proposed use of the data has been approved by an independent ethics review committee for this purpose. Further inquiries can be directed to the corresponding author.

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