

Effects of Postnatal Hydrocortisone Treatment on Cytokine Profile in Preterm Infants at Risk of Bronchopulmonary Dysplasia

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Abstract

Systemic hydrocortisone administration has been widely used in preterm infants who are at a risk of bronchopulmonary dysplasia (BPD). However, the effects of hydrocortisone on cytokine profiles have not been examined. We aimed to investigate the effects of postnatal hydrocortisone treatment on serum cytokine levels in extremely preterm infants at risk for BPD. In 29 extremely preterm infants (born at less than 28 weeks of gestational age), we obtained serum from blood samples collected during an early phase (5–20 days) and a late phase (28–60 days) after birth. We measured the levels of proinflammatory cytokines (tumor necrosis factors α and β , interleukin [IL]-1 β , and IL-6), T-helper (Th) 1 cytokines (interferon- γ , IL-2, and IL-12p70), Th2 cytokines (IL-4, IL-5, and IL-10), Th17 cytokine IL-17A, and chemokine IL-8. We found that serum IL-6 and IL-8 levels were significantly higher during the early phase than during the late phase (both $P = 0.03$). Other cytokines concentrations did not change between the phases. Thirteen infants (45%) received systemic hydrocortisone treatment at a median age of 15 days (IQR 10.0–21.5) after birth due to respiratory deterioration, after which the serum IL-6 levels significantly decreased ($P = 0.04$). Median duration of treatment was 16.0 (IQR 8.0–34.5) days.

Conclusion: Extremely preterm infants show high serum IL-6 and IL-8 levels in the early phase of life. Moreover, postnatal systemic hydrocortisone treatment might suppress IL-6 overproduction.

What Is Known?

- Although bronchopulmonary dysplasia (BPD) in preterm infants is a multifactorial disease, inflammation plays a major role in its pathogenesis.
- Systemic hydrocortisone is often used in preterm infants at risk of BPD, but prevention of BPD is still difficult.

What is new?

- Serum IL-6 and IL-8 levels were significantly higher during the early phase (5–20 days) than during the late phase (28–60 days) after birth in extremely preterm infants.
- Postnatal hydrocortisone for respiratory deterioration significantly reduced serum IL-6 levels.

Introduction

Bronchopulmonary dysplasia (BPD) is a disorder that causes morbidity and mortality among extremely preterm infants [1]. Moreover, BPD leads to various long-term complications, such as respiratory disease, pulmonary hypertension, and neurological developmental impairment during early childhood that can last into adolescence or even adulthood [2]. Although advances in neonatal care have improved the survival rate of extremely low-birth-weight infants, the rates of BPD have not improved [3]. Many factors influence the development of BPD, including prematurity, inflammation, infection, hyperoxia, mechanical ventilation, and genetic predisposition. Lung inflammation is thought to be particularly involved in the

development and exacerbation of BPD [3], and several studies have shown that cytokines, such as proinflammatory, T-helper (Th) 1 and Th2 cytokines, play a crucial role in the etiology of BPD in extremely preterm infants [4-8].

Treatment of BPD involves ventilation management and administration of various agents, such as surfactants, steroids, caffeine, nitric oxide, and vitamin A [9]. However, effective management and prevention of BPD remain challenging [9]. Postnatal corticosteroids may restrict inflammation and improve lung function in infants with established BPD. Indeed, until the early 2000s, dexamethasone was used widely for prevention and treatment of BPD. However, several studies suggest that postnatal dexamethasone could be associated with the increased risk of neurodevelopmental impairment [10]. As a result, clinicians refrained from using dexamethasone and used hydrocortisone as an alternative [11]. Multicenter randomized clinical trials have recently examined whether the use of systemic postnatal hydrocortisone treatment improves BPD and death [12; 13]. Baud et al. have shown that early (on the first day) low-dose hydrocortisone treatment improved survival without BPD in extremely preterm infants [12]. However, other trials have shown that hydrocortisone treatment between 7 and 14 days after birth did not improve the rate of death or BPD among mechanically ventilated very preterm infants [13]. It is still difficult to prevent the development of BPD, and thus precise indications, dosages, and duration of hydrocortisone treatment are being investigated [14].

In vitro studies have shown that steroids suppress the expression of inflammatory cytokines in cord blood neutrophils [15; 16] and change cytokine profiles in tracheobronchial aspirate fluids [17; 18]. However, there is little evidence on how hydrocortisone affects systemic inflammatory regulation in preterm infants with respiratory impairment.

We hypothesized that systemic hydrocortisone could regulate the production of excess proinflammatory cytokines, thereby suppressing lung damage in extremely preterm infants. We conducted a retrospective single-center study in a neonatal intensive care unit (NICU) to investigate the cytokine profiles in extremely preterm infants during their first two postnatal months and the effects of postnatal hydrocortisone treatment on serum cytokine levels in infants at risk for BPD.

Materials And Methods

Study design and patients

The study was carried out between January 2015 and December 2019 and involved babies in the NICU of Toyama University Hospital, Japan. This retrospective study was approved by the local ethics review committee for medical research (No. R2019175) and was performed in accordance with the Declaration of Helsinki.

Extremely preterm infants born at less than 28 weeks of gestational age were eligible. Those with major congenital anomalies or who died in the NICU were excluded from the study. Infants who had infections

or who underwent surgical treatment were also excluded because these conditions are strongly associated with changes in cytokine expression.

Steroid therapy

Our indication for hydrocortisone administration was respiratory deterioration that required fraction of inspired oxygen (FiO_2) >0.40 for intubated preterm infants. Hydrocortisone was generally not started within the first week of life due to concerns related to the risk of long-term neurological impairment. Hydrocortisone was most frequently initiated at 2 mg/kg per day, and tapering of the dose was attempted for 7 days after the start of treatment; however, there was no precise protocol for tapering of the dose. Therefore, neonatologists administered hydrocortisone at their own discretion.

Cytokine assay

Serum was separated from blood samples collected at two time points—5 to 20 days after birth (early phase) and 28 to 60 days after birth (late phase)—and then stored at -20°C until analysis. Cytokines were investigated using multiplex cytometric bead array technology. In each phase, the concentrations of 12 cytokines were measured and analyzed: proinflammatory cytokines (tumor necrosis factors α and β , interleukin [IL]-1 β , and IL-6), Th1 cytokines (interferon- γ , IL-2, and IL-12p70), Th2 cytokines (IL-4, IL-5, and IL-10), Th17 cytokine IL-17A, and chemokine IL-8. Samples were prepared for flow cytometric analysis with the Aimplex Human Th1/Th2/Th17 12-Plex panel kit (Aimplex Biosciences, Pomona, CA, USA) according to the manufacturer's instructions. Flow cytometry was performed with a Cytomics FC 500 (Beckman Coulter, Indianapolis, IN, USA). Cytokine levels between the early and late phase were compared. Analyses were also performed in serum samples of late-preterm babies born at 34–35 weeks' gestational age as controls for extremely preterm infants. In addition, cytokine levels and the ratio of early-to-late phase were compared in infants who received postnatal hydrocortisone versus those who did not.

Prenatal data

Maternal data were retrospectively obtained from mothers' medical records. These data included maternal age; mode of delivery; the presence of preterm premature rupture of membrane, clinical chorioamnionitis, histological chorioamnionitis, and funisitis; and antenatal administration of corticosteroids. Premature rupture of membrane was defined as a membrane rupture prior to the onset of labor. Clinical chorioamnionitis was defined as the combination of maternal fever and any of the following: maternal tachycardia, uterine tenderness, malodorous amniotic fluid, or maternal leukocytosis. Histological chorioamnionitis and funisitis were defined as the presence of polymorphonuclear leukocytes in fixed placenta and umbilical cord tissue, respectively.

Neonatal data

Neonatal data were retrospectively obtained from babies' medical records. These data included gestational age, birth weight, sex, Apgar score at 5 min, the presence of respiratory distress syndrome, BPD, retinopathy of prematurity, intraventricular hemorrhage grade III or IV, and periventricular leukomalacia, and whether they received home oxygen therapy. BPD was defined as oxygen dependency or positive pressure support at 36 weeks' postmenstrual age. Respiratory distress syndrome was defined as neonates requiring pulmonary surfactant therapy and retinopathy of prematurity as changes in the eyes requiring treatment. Intraventricular hemorrhage and periventricular leukomalacia were diagnosed based on MRI of the brain.

Statistical analysis

All data were analyzed using JMP statistical software (JMP 13.0.0, SAS Institute Inc, USA). Categorical variables were described as relative frequency (%). Median and interquartile ranges (IQRs) were used to present numerical data. The data were tested for normality using the Shapiro–Wilk test and found to be non-normally distributed, hence differences in cytokine levels between the early and late phase were assessed using the Wilcoxon signed rank test. Differences between steroid-treated and non-treated groups were assessed using the Mann–Whitney *U* test, chi-square test, or Fisher's exact test, as appropriate. $P < 0.05$ was considered statistically significant.

Results

During the study period, 48 babies were born at <28 weeks' gestational age (Fig. 1). Eighteen babies were excluded because of surgical operation ($n = 9$), congenital anomaly ($n = 4$), infection ($n = 4$), and death in the NICU ($n = 1$). One serum sample was lost. The remaining 29 babies were included in the study; median gestational age was 26.1 weeks (IQR 25.1–27.1 weeks) and birth weight was 791 (658–918) g. The early and late phase serum samples were taken at a median of 11 (7–14) days and 37 (31–42) days after birth, respectively. Eight late-preterm babies were also included with a median gestational age of 34.6 (IQR 34.5–35.4) weeks and birth weight of 2128 (1834–2381) g. The late-preterm babies had no respiratory symptoms and the serum samples were taken at a median of 13.5 (13.0–14.8) days after birth (ie, the early phase).

Among extremely preterm neonates, the level of IL-6 was significantly higher in the early phase than in the late phase (median 36.4 [IQR 30.5–120] pg/ml vs 26.7 [25.0–30.6] pg/ml, $P = 0.03$), as was that of IL-8 (120 [113–395] pg/ml vs 101 [74.0–162] pg/ml, $P = 0.03$) (Table 1). The levels of IL-6 and IL-8 in early phase in late-preterm neonates were 27.5 (26.4–31.8) pg/ml and 41.5 (33.1–53.0) pg/ml, respectively, and were significantly lower than those in extremely preterm neonates ($P = 0.009$ and $P < 0.0001$, respectively). Concentrations of the other cytokines, such as the Th1, Th2, and proinflammatory cytokines, were low and did not change between the early and the late phases (Table 1).

Postnatal hydrocortisone therapy for respiratory deterioration was given to 13 infants (45%). The median age (IQR) at which the treatment began was 15.0 (10.0–21.5) days. All 13 babies started treatment after

the early phase blood samples were collected. The median duration of hydrocortisone administration was 16.0 (IQR 8.0–34.5) days. Perinatal characteristics and neonatal complications are shown in Table 2. Maternal information was not significantly different between the groups. However, birth weight in the steroid group was significantly lower than that in the nonsteroid group (median 740 [IQR 507–843] g vs 889 [685–968] g, $P = 0.04$). The percentage of BPD was higher in the steroid group than in the nonsteroid group (85% vs 31%, $P = 0.008$). The levels of IL-6 and IL-8 in the steroid group tended to be higher than those in the nonsteroid group in the early phase, but not significant (median IL-6 66.1 [IQR 32.1–175.9] pg/ml vs 33.6 [28.3–52.0] pg/ml, $P = 0.13$; IL-8 241.4 [187.6–491.6] pg/ml vs 173.6 [76.2–242.4] pg/ml, $P = 0.07$) (Fig. 2a, supplementary Fig. 1a). The ratio of IL-6 for the early-to-late phase was significantly lower in the steroid group than in the nonsteroid group (median 0.46 [IQR 0.18–0.81] pg/ml vs 0.89 [0.49–0.99] pg/ml, $P = 0.04$) (Fig. 2b). This result indicated that serum IL-6 levels were significantly reduced after starting hydrocortisone treatment. However, the ratio for IL-8 was not significantly different between these groups (supplementary Fig. 1b).

Discussion

We found that concentrations of IL-6 and IL-8, but not other cytokines, were higher in the early postnatal phase than in the late phase. In addition, hydrocortisone treatment given for respiratory deterioration did not prevent development of BPD, but it suppressed the overproduction of IL-6.

Increasing evidence suggests that BPD results from an imbalance between proinflammatory and anti-inflammatory mechanisms, in favor of a proinflammatory response [3]. Chemokine IL-8 and the proinflammatory cytokines TNF- α and IL-6 are crucial mediators in the early inflammatory response [3]. These cytokines are synthesized in alveolar macrophages, epithelial cells, fibroblasts, type II pneumocytes, and the endothelial cells after stimulation by hypoxia, hyperoxia, endotoxin, microorganisms, and biophysical factors such as barotrauma and volutrauma [3]. Very-low-birth-weight infants who develop BPD have high concentrations of proinflammatory cytokines in the alveolar lavage fluid [19]. Ambalavanan and colleagues investigated serum cytokine profiles during the first 28 days after birth in 1,062 extremely preterm infants and found that infants who died or developed BPD had higher concentrations of IL-1 β , IL-6, IL-8, and interferon γ but lower concentration of IL-17 than the babies who survived without BPD [4]. Furthermore, cytokine profiles might differ between infants who develop classical and atypical forms of BPD [20]. In our study, we noted that the levels of IL-6 and IL-8 were significantly higher during the early phase than during the late phase in extremely preterm infants, and were higher than those in the early phase in late-preterm infants as well. Therefore, proinflammatory cytokines and chemokines were elevated in the acute phase of extremely preterm infants and may be associated with lung injury. It might be appropriate to measure serum cytokines in considering the cause and pathophysiology of BPD. Our study showed similar results to previous reports for IL-6 and IL-8 [4; 20] but no changes were seen in levels of other cytokines between early and late phase, probably due to the small number of cases.

Multicenter randomized clinical trials have examined whether the use of prophylactic systemic hydrocortisone therapy reduces the risk of BPD and prevents death [12; 13]. Early low-dose hydrocortisone administration during the first 10 days of life has been associated with superior survival without development of BPD at 36 weeks' postmenstrual age [12]. In contrast, among mechanically ventilated infants, administration of hydrocortisone between 7 and 14 days after birth did not improve the outcome of death or BPD [13]. We believe that routine hydrocortisone therapy for all extremely preterm infants is not recommended because the potential benefits do not outweigh the known complications such as hyperglycemia, hypertension, gastrointestinal perforation and adverse neurodevelopmental outcomes for patients who do not need treatment [14; 21]. However, considering that the extremely preterm infants with the poorest respiratory status tended to have higher serum IL-6 and IL-8 levels in the early phase and showed significantly lower early-to-late phase ratio of IL-6, we suggest that investigating cytokine profiles could stratify the risk of BPD and the suitability of starting postnatal hydrocortisone.

In vitro studies on the mechanisms of action of steroids have shown that proinflammatory cytokines, such as TNF- α and IL-1 β , were suppressed in cord blood polymorphonuclear leukocytes by coculture with dexamethasone [16]. Hydrocortisone has also been shown to inhibit the release of IL-8 and macrophage inflammatory proteins from polymorphonuclear neutrophils in neonates [15]. Analysis of bronchoalveolar lavage fluid has shown that dexamethasone therapy reduced the level of inflammatory cytokines, vascular endothelial growth factor, and transforming growth factor beta 1 [17; 18]. In this study, we indicated that the early-to-late phase IL-6 ratio was significantly lower in the steroid group than in the non-steroid group. This result implies that serum IL-6 levels were significantly reduced after hydrocortisone treatment in infants at risk for BPD. Our study suggested that postnatal hydrocortisone administration suppressed systemic IL-6 overproduction in the acute phase of respiratory deterioration in extremely preterm infants. This result was consistent with previous studies using cultured cells and bronchoalveolar lavage fluid [3; 19].

Our study has strengths and some limitations. This is the first study to evaluate the association between postnatal hydrocortisone treatment and serum cytokine profiles in extremely preterm infants. It was possible to track changes over time by using serum from blood samples collected at two timepoints. By using multiplex cytometric bead array technology, we were able to investigate many cytokines from a small amount of blood. However, our study was retrospective, and the number of cases was small. Further investigations are warranted to consider how postnatal hydrocortisone administration changes cytokine profiles and to assess the predictive value of cytokine measurement.

In conclusion, extremely preterm infants at risk for BPD have high serum IL-6 and IL-8 levels in the early phase of life. Our study indicated that postnatal hydrocortisone treatment can suppress systemic IL-6 production and might work to reduce inflammatory damage to the premature lungs.

Abbreviations

BPD, bronchopulmonary dysplasia

IL, interleukin

IVH, intraventricular hemorrhage

NICU, neonatal intensive care unit

PROM, premature rupture of membrane

PVL, periventricular leukomalacia

RDS, respiratory distress syndrome

ROP, retinopathy of prematurity

Th, T helper

TNF, tumor necrosis factor

Declarations

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Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest.

Availability of data and material: Not applicable

Code availability: Not applicable

Authors' contributions: KT designed the study and analyzed the data. MN, SI, YK and MM collected the data. TY designed the study and analyzed the data. All authors were involved in writing the manuscript and approved the final version.

Ethics approval and consent to participate: All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics approval was received from Toyama University Hospital's Ethics Committee. All participants gave consent prior to beginning of the study.

Consent for publication: Written informed consent was obtained from the parents of the patients for publication of this manuscript.

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Tables

Table 1 Comparison of cytokine levels between early (day 5–20) and late (day 28–60) phase

	Early phase	Late phase	P value
TNF- α	23.7 (23.6–24.4)	23.7 (23.6–23.9)	0.11
TNF- β	3.7 (2.6–5.3)	3.1 (2.2–4.2)	0.11
IL-1 β	12.4 (12.0–13.1)	12.9 (12.2–13.5)	0.39
IL-6	36.4 (30.5–120)	26.7 (25.0–30.6)	0.03
INF- γ	24.7 (21.7–29.5)	24.1 (20.6–27.3)	0.41
IL-2	20.6 (19.1–22.8)	19.4 (18.6–20.9)	0.10
IL-12p70	3.3 (2.1–4.4)	3.1 (1.9–5.0)	0.17
IL-4	12.2 (11.2–13.5)	11.7 (11.1–14.1)	0.92
IL-5	25.3 (24.5–25.9)	25.1 (24.4–26.2)	0.93
IL-10	8.4 (7.6–11.2)	8.3 (7.9–10.5)	0.68
IL-17A	0.0 (0.0–1.8)	0.0 (0.0–0.0)	0.18
IL-8	200 (113–395)	101 (74.0–162)	0.03

IL, interleukin. INF, interferon. TNF, tumor necrosis factor. Values are median (interquartile range). The range is pg/ml.

Table 2 Maternal and infant characteristics of subjects with and without postnatal steroid treatment

	Steroid group (n=13)	Non-steroid group (n=16)	P value
Maternal age	31 (25–36)	34 (28–37)	0.45
Cesarean section	9 (69)	15 (94)	0.14
Preterm PROM	4 (31)	8 (50)	0.45
Clinical CAM	1 (8)	3 (19)	0.61
Histological CAM (Grade 2, 3)	7 (54)	9 (56)	0.90
Funisitis	5 (38)	7 (44)	0.77
Antenatal steroid	9 (69)	10 (63)	0.99
Gestational age	25.6 (23.4–26.5)	26.6 (25.2–27.5)	0.10
Birth weight (g)	740 (507–843)	889 (685–968)	0.04
SGA	4 (31)	2 (13)	0.36
Female	10 (77)	6 (38)	0.06
Apgar score (5 min)	5 (4.5–6.5)	5 (4–6)	0.77
Surfactant treatment	13 (100)	14 (88)	0.49
BPD	11 (85)	5 (31)	0.008
Home oxygen therapy	5 (38)	2 (13)	0.19
PVL	0 (0)	1 (6)	0.99
IVH (Grade 3, 4)	0 (0)	1 (6)	0.63
ROP treatment	4 (31)	5 (31)	0.99

BPD, bronchopulmonary dysplasia. CAM, chorioamnionitis. IVH, intraventricular hemorrhage. PROM, premature rupture of membrane. PVL, periventricular leukomalacia. ROP, retinopathy of prematurity. SGA, small for gestational age. Values are number (percentage) or median (interquartile range).

Figures

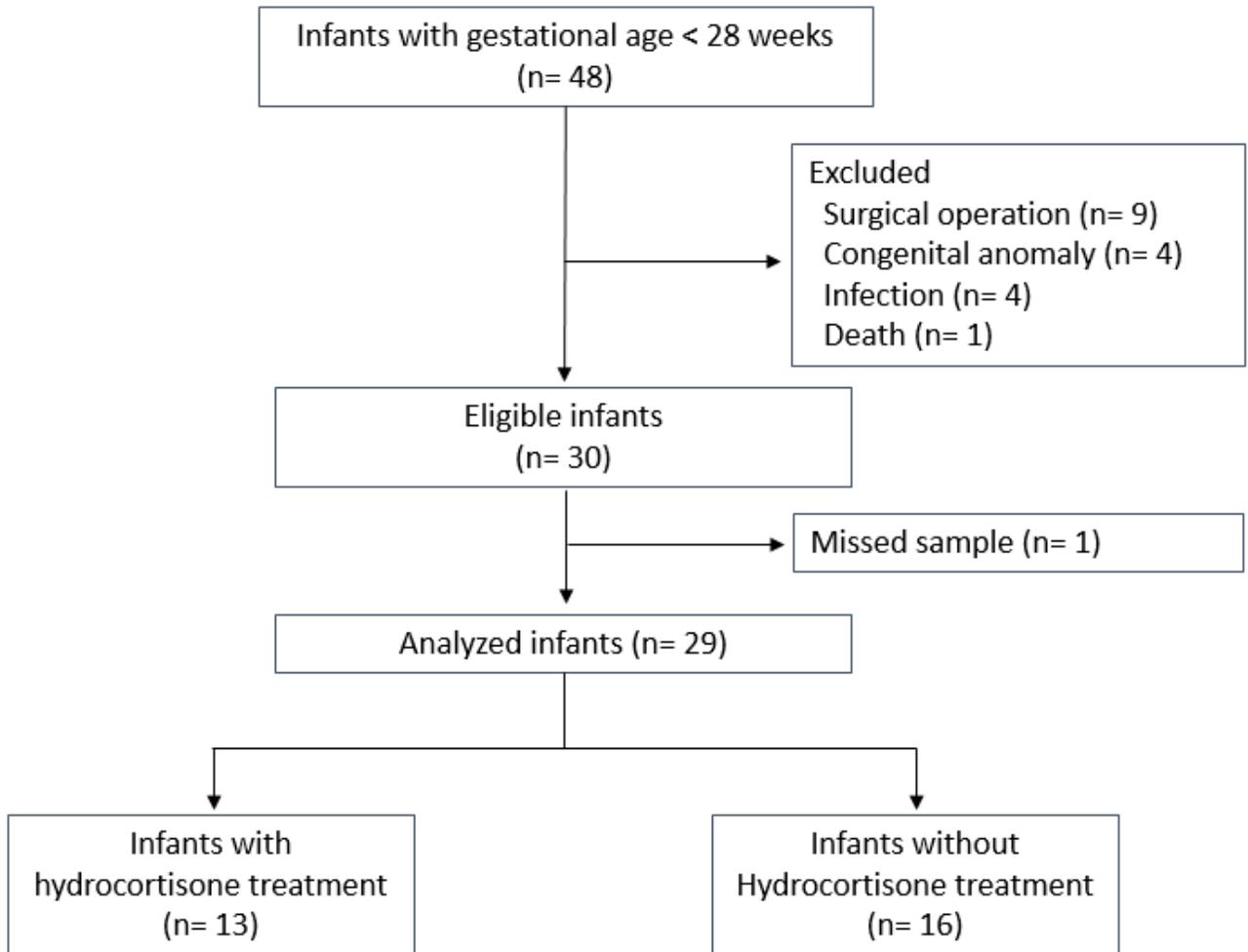


Figure 1

Flow chart of the study population

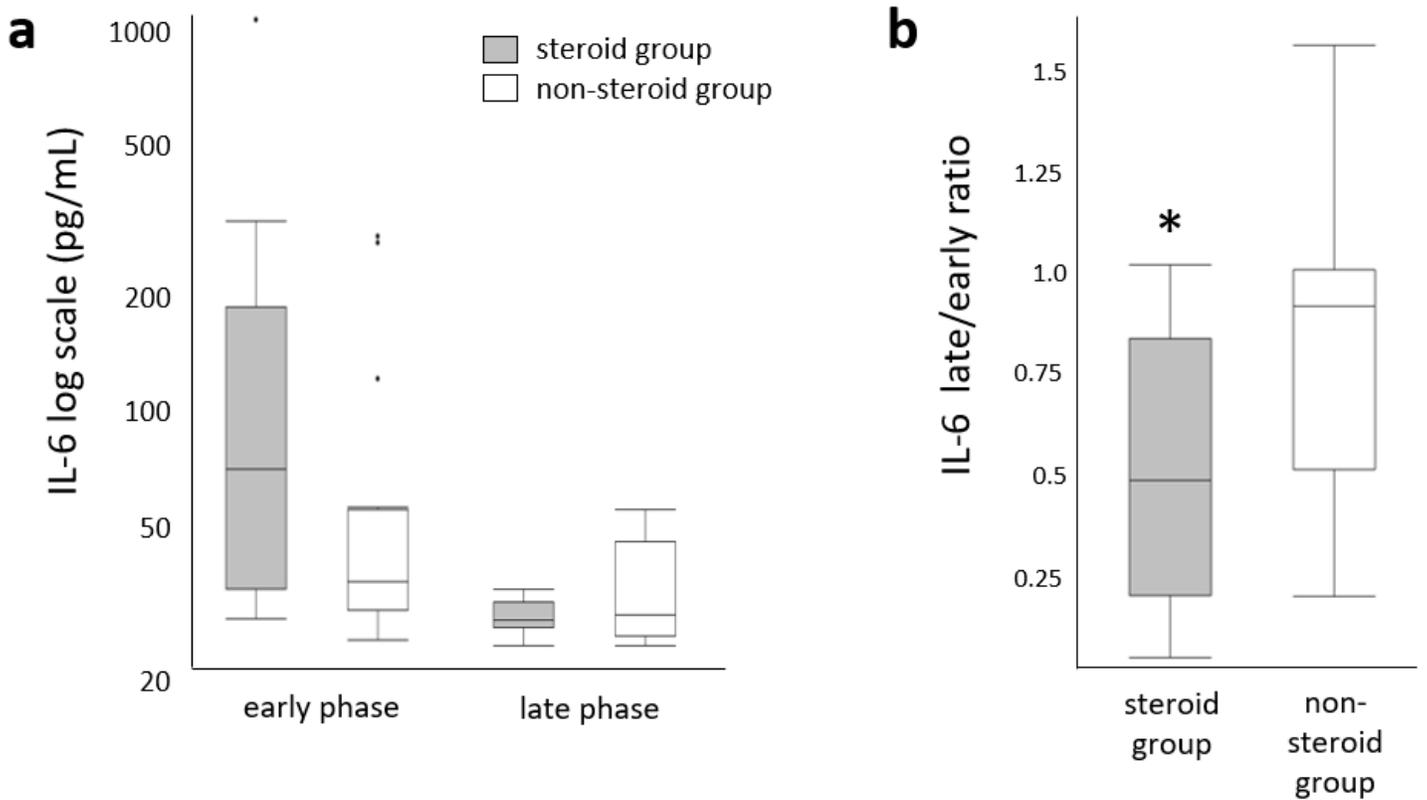


Figure 2

Comparison of serum IL-6 between the steroid and nonsteroid groups. a, Box plot analysis of serum IL-6 during early (5–20 days after birth) and late (28–60 days after birth) phases of life in extremely preterm infants with or without hydrocortisone administration. b, Box plot analysis of early-to-late-phase ratio of IL-6 between the steroid and the nonsteroid groups. The line in the middle of each box represents the median. The lower and the upper edges of the box are the first and the third quartile, respectively. Outliers are indicated by dots. Significant box plots ($p < 0.05$) are marked with *.

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