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Unsatisfactory Short-Term Neurodevelopmental Outcomes of Preterm Infants Who Received Polymyxin B-Immobilized Fiber Column-Direct Hemoperfusion for Septic Shock

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Sepsis and septic shock are associated with high mortality and neurodevelopmental impairment in preterm infants. Recently, endotoxin and mediator removal using a polymyxin B-immobilized fiber column for direct hemoperfusion (PMX-DHP) has been used for the management of septic shock even in neonates. Although early withdrawal from shock with PMX-DHP contributes to survival, its effect on neurodevelopment after discharge is unclear. This study aimed to examine short-term neurodevelopmental impairment in preterm infants with septic shock who were treated with PMX-DHP. We retrospectively assessed five infants who received treatment with PMX-DHP (median 25.5 [interquartile range: 24.8-28.3] weeks and 817 [interquartile range: 667-954] g). Neurodevelopmental outcomes were assessed with the Kyoto Scale of Psychological Development 2001 at a median 34.5 (interquartile range: 29.5-44.5) months of corrected age after discharge. The short-term neurodevelopmental prognosis of preterm infants treated with PMX-DHP for septic shock was delayed (overall developmental quotient < 70) with an average quotient of 57.3. Furthermore, four (80%) of five patients presented with intraventricular hemorrhage and another four (80%) with periventricular leukomalacia. In conclusion, preterm infants with septic shock treated with PMX-DHP had unsatisfactory short-term neurodevelopmental outcomes. Hence, the effect of PMX-DHP in improving neurodevelopmental prognosis even in preterm infants with septic shock should be further evaluated.

Keywords: Kyoto Scale of Psychological Development; neurodevelopmental impairment; polymyxin B-immobilized fiber column-direct hemoperfusion; preterm infants; septic shock
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Introduction

Although the survival rate of premature infants has significantly increased within the last two decades, their neurodevelopmental prognoses are still unsatisfactory (Itabashi et al. 2009; Robertson et al. 2009). In particular, very-low-birth-weight infants (< 1,500 g birth weight) and/or extremely preterm infants (< 28 weeks gestational age) have a high risk of neurodevelopmental impairment (NDI), including cognitive and psychomotor delay (Larroque et al. 2008). In addition, the incidence of infection is 3-10 times higher in preterm low-birth-weight infants than in full-term normal-birth-weight infants during the neonatal period (Weston et al. 2011). Meanwhile, severe sepsis and neurodevelopmental outcomes of surviving preterm infants have been correlated to cerebral white matter injury, intracranial hemorrhage, most commonly intraventricular hemorrhage, and periventricular leukomalacia (Alshaikh et al. 2013). Neonatal sepsis is a leading cause of morbidity and mortality and is associated with significant healthcare utilization among infants after discharge from the neonatal intensive care unit (NICU).

By contrast, most infants who die of sepsis experience refractory shock with a high incidence of mortality within the first 48-72 hours of treatment (Weiss et al. 2020). Thus, early diagnosis and treatment with antibiotics are important in optimizing outcomes in sepsis. Recently, endotoxin and mediator removal using a polymyxin B-immobilized fiber column for direct hemoperfusion (PMX-DHP) has been utilized for severe septic shock even in neonates (Nishizaki et

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al. 2016). We have previously reported the effect of PMX-DHP on septic shock in preterm infants (Nishizaki et al. 2020a). Our results showed that PMX-DHP for early-onset sepsis (sepsis occurring ≤ 72 h after birth) had a significantly lower mortality rate than that for late-onset sepsis (occurring > 72 h after birth). Although early withdrawal from shock with PMX-DHP contributes to survival upon discharge, its effect on neurodevelopment has not been described. Therefore, we conducted a single-center retrospective cohort study to validate for early neurodevelopmental outcomes in surviving preterm infants after PMX-DHP for septic shock.

Materials and Methods

Ethics approval and consent

This study was approved by the Institutional Ethics Committees of Juntendo University Urayasu Hospital (Approval No. 2-037), and was conducted in accordance with applicable laws and regulations, good clinical practice, and tenets of the Declaration of Helsinki (World Medical Association 2013). Written informed consents were not required due to the retrospective nature of the study. The participants had the right to opt out of the study at any time.

Study population

We evaluated 1,465 infants admitted to the Juntendo University Urayasu Hospital, Department of NICU, Chiba, Japan, from January 2013 to December 2018. We retrospectively evaluated all patients with positive blood culture results upon admission. Of all hospitalized infants, 49 had sepsis confirmed via blood culture. Among them, 11 received PMX-DHP for early- or late-onset septic shock according to a procedure in a previous study (Nishizaki et al. 2020a). The inclusion criteria for PMX-DHP were as follows: (1) The first diagnosis was sepsis; (2) Met the presence of systemic inflammatory response syndrome (SIRS) based on the Goldstein et al. (2005) criteria; and (3) Required catecholamine (> 10 μg/kg/min) and/or serum interleukin (IL)-6 > 500 pg/mL measured using a semi quantitative measurement kit (STICKELISA® and RAY-FAST®; Toray, Tokyo, Japan). Infants with organ bleeding prior to the induction of PMX-DHP were excluded. The PMX-DHP procedure and apparatus used were similar to those utilized in a previous study (Nishizaki et al. 2016, 2020a).

Developmental assessment

The developmental level of patients was assessed using the Kyoto Scale of Psychological Development 2001 (KSPD) (Society for the Kyoto Scale of Psychological Development Test 2008). The KSPD is a standardized developmental test particularly for children that has been widely used in Japan. It is used to assess posture-motor (P-M) area (fine and gross motor functions), cognitive-adaptive (C-A) area (nonverbal reasoning and visuospatial perceptions), and language-social (L-S) area (interpersonal relationships, socialization, and verbal abilities). The sum of the three scores was then converted to a developmental quotient (DQ) (Aoki et al. 2016). The mean and standard deviation (SD) of the DQ were 100.6 and 13.4, respectively. A DQ score of KSPD < 70, which represents a 70% achievement of standardized performance for chronological age (CA), was considered a significant delay. In addition, a DQ score of KSPD < 70 is equivalent to a Bayley III cognitive score of < 85 (Kono et al. 2016).

The test can identify an examinee's overall developmental age (DA) and DQ, which is calculated as follows: DQ = DA/CA × 100.

In this study, the overall DQ was used for the main outcomes because DQ signifies the children's age, which is an independent variable. The KSPD was administered at each local welfare center or rehabilitation center where the patient was managed by a trained clinical psychologist independent of the authors. Based on the abovementioned reasons, the KPSD DQ is considered a useful parameter for evaluating a child's development in Japanese clinical setting.

Data collection

We collected data from medical records, which included maternal age; presence of conditions such as chorioamnionitis, premature rupture of the membranes, and non-reassuring fetal status; treatment with perinatal steroids; delivery method; gestational age at birth; birth weight; sex; Apgar score at 5 min after birth; treatment with postnatal steroids; invasive ventilation; surfactant replacement; nitric oxide inhalation; antibiotic administration; mean blood pressure; respiratory rate; heart rate; core temperature; data of blood examination; catecholamine index; duration and frequency of PMX-DHP treatment; blood culture results; age at discharge; adverse events during admission including patent ductus arteriosus; necrotizing enterocolitis; retinopathy of prematurity; intraventricular hemorrhage; periventricular leukomalacia; hypoxic-ischemic encephalopathy; chronic lung disease at 36 weeks of post-conceptual age; presence of epilepsy; hearing impairment; presence of home oxygen therapy; requirement of tracheostomy at discharge and feeding tube at discharge; presence of cerebral palsy; and KSPD score.

Disseminated intravascular coagulation (DIC) score was defined as Japanese Guideline of Diagnosis and Clinical Management for Neonatal DIC (Shirahata et al. 2016). Patent ductus arteriosus and retinopathy of prematurity were defined as requirement of ligation and photocoagulation, respectively (Kindler et al. 2017; Agarwal and Jalali 2018). Necrotizing enterocolitis was defined as grade 2 or 3 according to modified Bell's staging (Bell et al. 1978). Intraventricular hemorrhage was diagnosed through a cranial ultrasonographic scan at bedside. The classification of intraventricular bleeding was based on the Papile's classification (Papile et al. 1978). Periventricular leukomalacia and hypoxic-ischemic encephalopathy were diagnosed

through brain magnetic resonance imaging by a radiologist before discharge. Cerebral palsy was defined as a non-progressive, non-transient central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture (Bax 1964).

Results were expressed as median and interquartile range (IQR) for continuous variables and as counts (%) for categorical variables.

Results

Fig. 1 shows the enrolment flow chart. Overall, 11 patients, including seven (64%) boys, received PMX-DHP. Seven patients (early-onset sepsis, 6; late-onset sepsis, 1) treated with PMX-DHP were discharged alive. Two patients were excluded from this study due to chromosomal anomaly and dropping out during follow-up. The final five patients were followed up every 1-4 months in an outpatient clinic, and they underwent neurodevelopmental assessment using KSPD. The overall median gestational age and birth weight of these patients were 25.5 (IQR: 24.8-28.3) weeks and 817 (IQR: 667-954) g, respectively.

Table 1 shows the baseline characteristics of mothers and infants. Nitric oxide was administered to three infants who had developed persistent pulmonary hypertension of the newborn before the start of PMX-DHP. All infants diagnosed with early-onset sepsis received PMX-DHP, and they survived until discharge. In 60% of patients, the causative agent was *Escherichia coli*. The median serum IL-6 concentration before treatment with PMX-DHP was extremely high (normal value: 4.0 pg/mL).

Table 2 lists the complications and statuses of the infants during admission and upon discharge. High-grade intraventricular hemorrhage (grades III-IV) was observed in four (80%) of five cases. Of these, three (75%) cases required a ventriculoperitoneal shunt after discharge. One infant developed intraventricular hemorrhage during PMX-DHP, whereas the remaining three infants developed intraventricular hemorrhage immediately after or a day after PMX-DHP.

The KSPD scores are shown in Fig. 2. The KSPD was conducted once between 22 and 67 (median: 34.5; IQR: 29.5-44.5) months. In two cases, the overall DQ could not be calculated. One patient was uncooperative during the

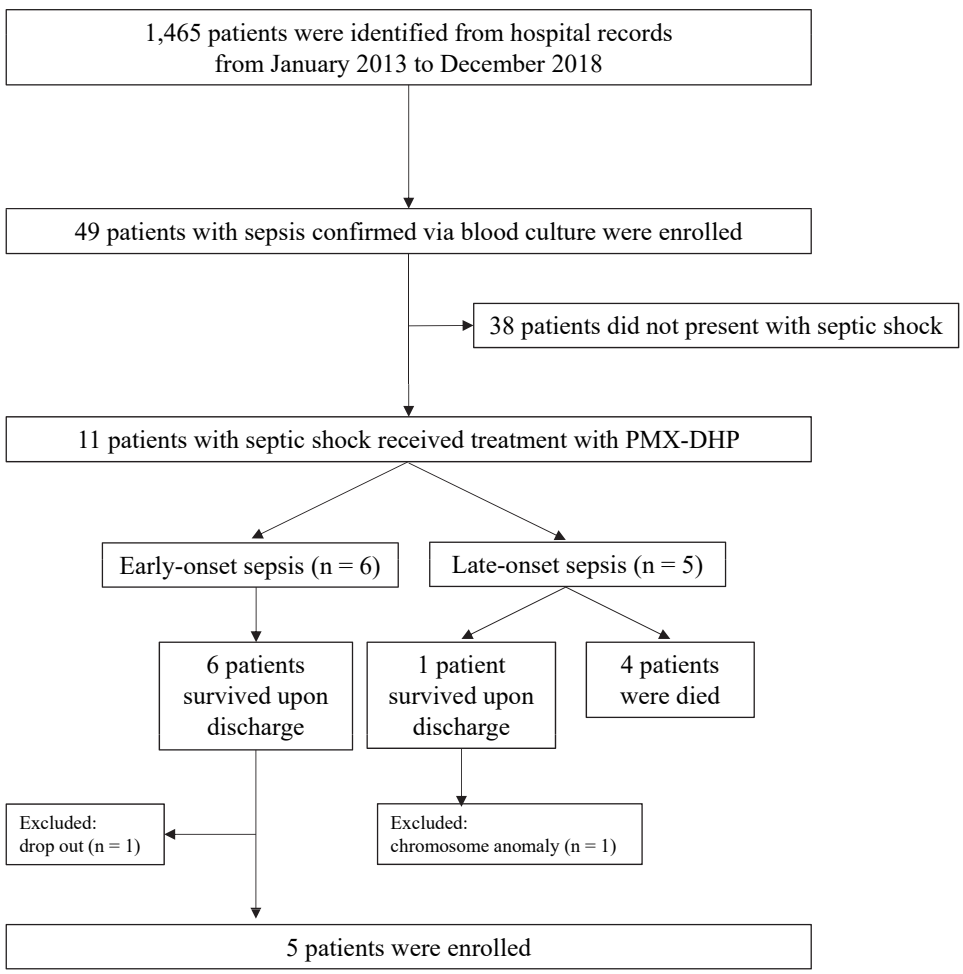

Fig. 1. Enrolment flow chart for this study.
PMX-DHP, polymyxin B-immobilized fiber column direct hemoperfusion.

Table 1. Baseline characteristics of patients before PMX-DHP.

	n = 5
Maternal characteristics	
Age (year), median (IQR)	34.5 (34.0-37.8)
Chorioamnionitis, *n* (%)	5 (100)
PROM, *n* (%)	4 (80)
NRFS, *n* (%)	3 (60)
Prenatal steroid administration, *n* (%)	3 (60)
Cesarean delivery, *n* (%)	4 (80)
Infant characteristics	
Gestational age (weeks), median (IQR)	25.5 (24.8-28.3)
Birth weight (g), median (IQR)	817 (667-954)
Boy, *n* (%)	2 (40)
Singleton, *n* (%)	5 (100)
Apgar score at 5 min., median (IQR)	5 (3.5-6.5)
Postnatal steroid administration, *n* (%)	2 (40)
Invasive ventilation, *n* (%)	5 (100)
Surfactant replacement, *n* (%)	5 (100)
NO inhalation, *n* (%)	3 (60)
Antibiotic administration, *n* (%)	5 (100)
Mean blood pressure (mmHg), median (IQR)	32.5 (21.0-34.3)
Respiration rate (breaths/min), median (IQR)	50 (44-70)
Heart rate (beats/min), median (IQR)	160 (149.5-175.5)
Core temperature (°C), median (IQR)	36.0 (35.9-36.8)
Leukocyte count (/μL), median (IQR)	2,200 (1,500-3,150)
Immature neutrophil > 10%, *n* (%)	4 (80)
Platelets count ($\times 10^4/\mu$L), median (IQR)	13.3 (9.6-16.7)
[a]DIC score, median (IQR)	3 (2-3)
C-reactive protein (mg/dL), median (IQR)	1.4 (0.7-5.1)
Lactate (mmol/L), median (IQR)	8.0 (2.5-9.8)
Interleukin-6 (pg/mL), median (IQR)	6,792 (5,000-10,000)
[b]CAI (μg/kg/min), median (IQR)	10 (3.5-20)
Frequency of PMX-DHP treatment (times), mean (± SD)	1.7 (± 0.5)
Total duration of PMX-DHP treatment (h), median (IQR)	5.7 (4.9-7.2)
Detected microorganisms from blood culture	
Escherichia coli	3 (60)
Enterobacter cloacae	1 (20)
Streptococcus agalactiae	1 (20)

[a]DIC score was defined as overt DIC (≥ 4 points), suspected DIC (3 points), and non-DIC(< 2 points) based on Guideline of Diagnosis and Clinical Management for Neonatal DIC.
[b]CAI was calculated as follows: (dose of dopamine and dobutamine) + (dose of noradrenaline and adrenaline) × 100.
PMX-DHP, polymyxin B-immobilized fiber column direct hemoperfusion; IQR, interquartile range; PROM, premature rupture of the membranes; NRFS, non-reassuring fetal status; SGA, small for gestational age; NO, nitric oxide; DIC, disseminated intravascular coagulation; CAI, catecholamine Index; SD, standard deviation.

whole test because of cerebral palsy, and the other had no C-A DA that could be converted at 22 months at the time of the assessment. In the analysis that excluded missing values, the mean overall DQ that could be evaluated was 57.3.

Discussion

To the best of our knowledge, this is the first report that evaluated the short-term neurodevelopmental outcome of preterm infants treated with PMX-DHP for septic shock. In accordance with the Japanese protocol for the follow-up of very-low-birth-weight infants, delayed, subnormal, and normal were defined as an overall DQ of < 70, 70-84, and ≥ 85, respectively (Kono et al. 2011; Kono 2020). Our results showed that all survivors treated with PMX-DHP had NDI

Table 2. Complications and status in infants.

	n = 5
During admission	
[a]Ligation of patent ductus arteriosus, *n* (%)	2 (40)
[b]Necrotizing enterocolitis, *n* (%)	0 (0)
[c]Retinopathy of prematurity, *n* (%)	3 (60)
Oxygen on day 28 of life, *n* (%)	3 (60)
At discharge	
Duration of hospitalization (days), median (IQR)	125 (111-151)
Corrected age (weeks), median (IQR)	45.5 (44.5-51.5)
[d]Intraventricular hemorrhage	
No blood, *n* (%)	1 (20)
Grade I - II, *n* (%)	1 (20)
Grade III - IV, *n* (%)	3 (60)
[e]Periventricular leukomalacia, *n* (%)	4 (80)
[f]Hypoxic ischemic encephalopathy, *n* (%)	1 (20)
[g]Chronic lung disease, *n* (%)	0 (0)
Epilepsy, *n* (%)	3 (60)
Hearing loss, *n* (%)	0 (0)
[h]Cerebral palsy, *n* (%)	1 (20)
HOT, *n* (%)	0 (0)
Tracheostomy, *n* (%)	0 (0)
Tube feeding, *n* (%)	0 (0)

[a]Patent ductus arteriosus was defined as a hemodynamically significant PDA on echocardiography.
[b]Necrotizing enterocolitis was defined as grade 2 or 3 according to modified Bells' staging.
[c]Retinopathy of prematurity was defined as stage 3 or more.
[d]Intraventricular hemorrhage was defined as the Papille's classification.
[e, f]Periventricular leukomalacia and Hypoxic ischemic encephalopathy were diagnosed as brain magnetic resonance imaging by radiologist.
[g]Chronic lung disease was defined as respiratory support beyond 36 weeks post-conceptual age.
[h]Cerebral palsy was defined as a non-progressive, non-transient central nervous system disorder characterised by abnormal muscle tone in at least one extremity and the abnormal control of movement and posture.
IQR, interquartile range; HOT, home oxygen therapy.

classified as delayed. According to an evaluation performed using the KSPD at 3 years of age among Japanese children born with very-low-birth-weight infants, DQ < 70 was only observed in 15.9% of 2,085 cases in 2003-2015 (Kono 2020). Meanwhile, in this study, the proportion of patients with DQ < 70 was high (75%). The high incidence of NDI may be attributed to the equally high incidence of intraventricular hemorrhage (80%) among the subjects. The timing of early-onset sepsis onset is commonly before 72 h after birth, which is also the risk period for developing intraventricular hemorrhage in preterm infants (Miller et al. 2005). We emphasize that strict control of the coagulation fibrinolysis system is important for the prevention of intraventricular hemorrhage. Anticoagulant administration during PMX-DHP should be monitored with an activated clotting time for strictly no more than 200 seconds. Abnormalities in the coagulation fibrinolysis system need to be addressed by fresh frozen plasma or platelet transfusion during PMX-DHP. Moreover, in the study, 80% of patients upon discharge presented with periventricular leukomalacia. Periventricular leukomalacia is a major cause of NDI and epilepsy. Although the cause of periventricular leukomalacia is still unknown, the presence of cytokines may be correlated with the development of white matter injury (Back et al. 2017). Interestingly, in this study, the serum IL-6 levels before induction of PMX-DHP were extremely high. Elevated IL-6 levels are associated with periventricular leukomalacia in infants born at < 32 weeks of gestation (Goepfert et al. 2004). Hence based on our results, both severe prematurity and hypercytokinemia can contribute to NDI. Meanwhile, the polymyxin B-immobilized fiber can remove inflammatory cells and circulating inflammatory mediators including IL-6 (Nishibori et al. 2009; Nishizaki et al. 2017). Although no standard indication criteria have been established for PMX-DHP for preterm infants with septic shock, the removal of inflammatory cytokines may improve not only the prognosis of mortality but also the adverse effects in the central nervous system. To achieve

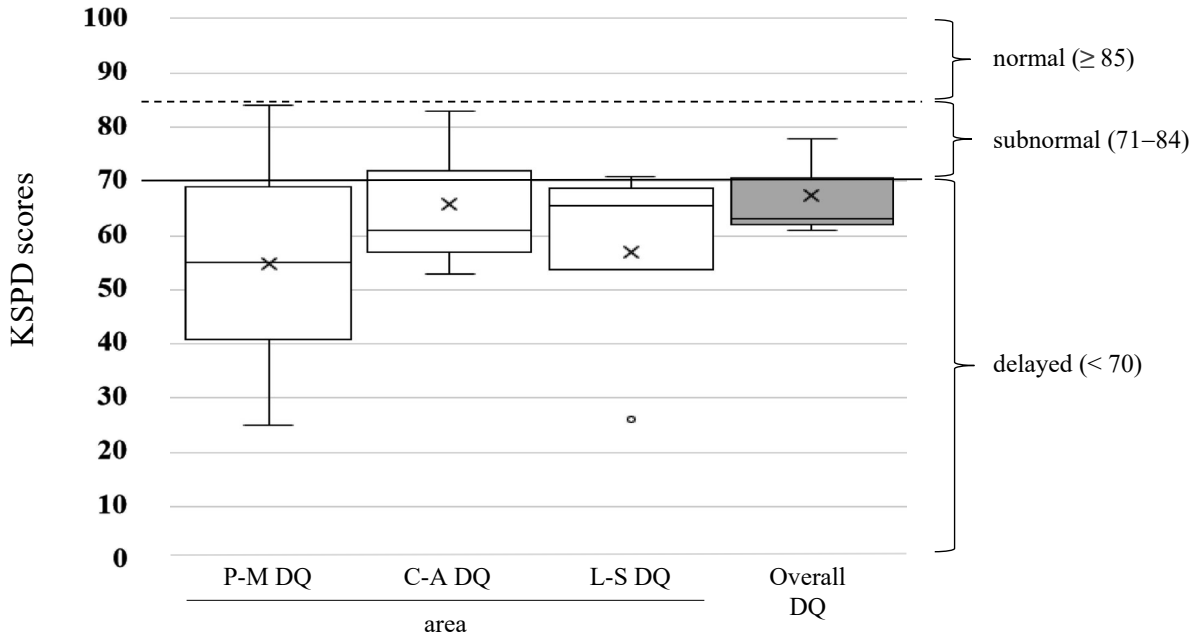

Fig. 2. Kyoto Scale of Psychological Development 2001 (KSPD) scores of the participants.
Values for the different areas were presented as median and interquartile range and were indicated as box-and-whisker plots. *Cross* (×) and *open circle* (○) represent the mean and an outlier, respectively.
P-M, posture-motor; C-A, cognitive-adaptive; L-S, language-social; DQ, developmental quotient.

intact survival in preterm infants with sepsis, the appropriate selection of indications for PMX-DHP can also improve neurodevelopment.

This study evaluated the prognosis of preterm infants using KSPD. We believe that KSPD is appropriate for the developmental assessment of Japanese children treated with PMX-DHP. Although there are several studies on treatment with PMX-DHP in adult patients worldwide, almost all case reports regarding the use of PMX-DHP for infants have been conducted by Japanese researchers (Nishizaki et al. 2020b). The reason is that the PMX-DHP column with a priming volume of 8 mL (Toraymyxin 01-R®; Toray Medical Co., Tokyo, Japan) is only available in Japan. Therefore, the use of PMX-DHP in foreign countries for infants with septic shock is still limited.

The study had several limitations. First, this was a retrospective study at a single center. Indeed, the number of neonatal hospitalizations was as low as 200 per year, and the number of infants eligible for PMX-DHP was approximately 1-2 cases per year. In addition, although patients survived neonatal sepsis, developmental assessment could not be performed on patients with cerebral palsy. Furthermore, hierarchical analysis using a statistical method could not be performed. Second, socioeconomic variables, such as race, medical insurance, parents' education level, and marital status, may affect cognitive function in infants. However, these socioeconomic variables were not assessed in this research. Third, we did not compare multiple KSPDs at different ages in each patient. The observation period at the outpatient clinic was cut short by the state of emergency declared by the Japanese government due to COVID-19, which placed a temporary restriction on the activities of welfare and rehabilitation centers, particularly after March 2020 (Furuse et al. 2020). Despite the above-mentioned limitations, this study revealed that the neurodevelopmental prognoses were not satisfactory.

In conclusion, preterm infants treated with PMX-DHP for septic shock showed unsatisfactory short-term neurodevelopmental outcomes. Methods for enforcing PMX-DHP should be discussed to improve neurodevelopmental prognosis in preterm infants.

Conflict of Interest

The authors declare no conflict of interest.

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