An investigation of the safety of a lipid emulsion in very-low-birth-weight infants based on cytokine levels

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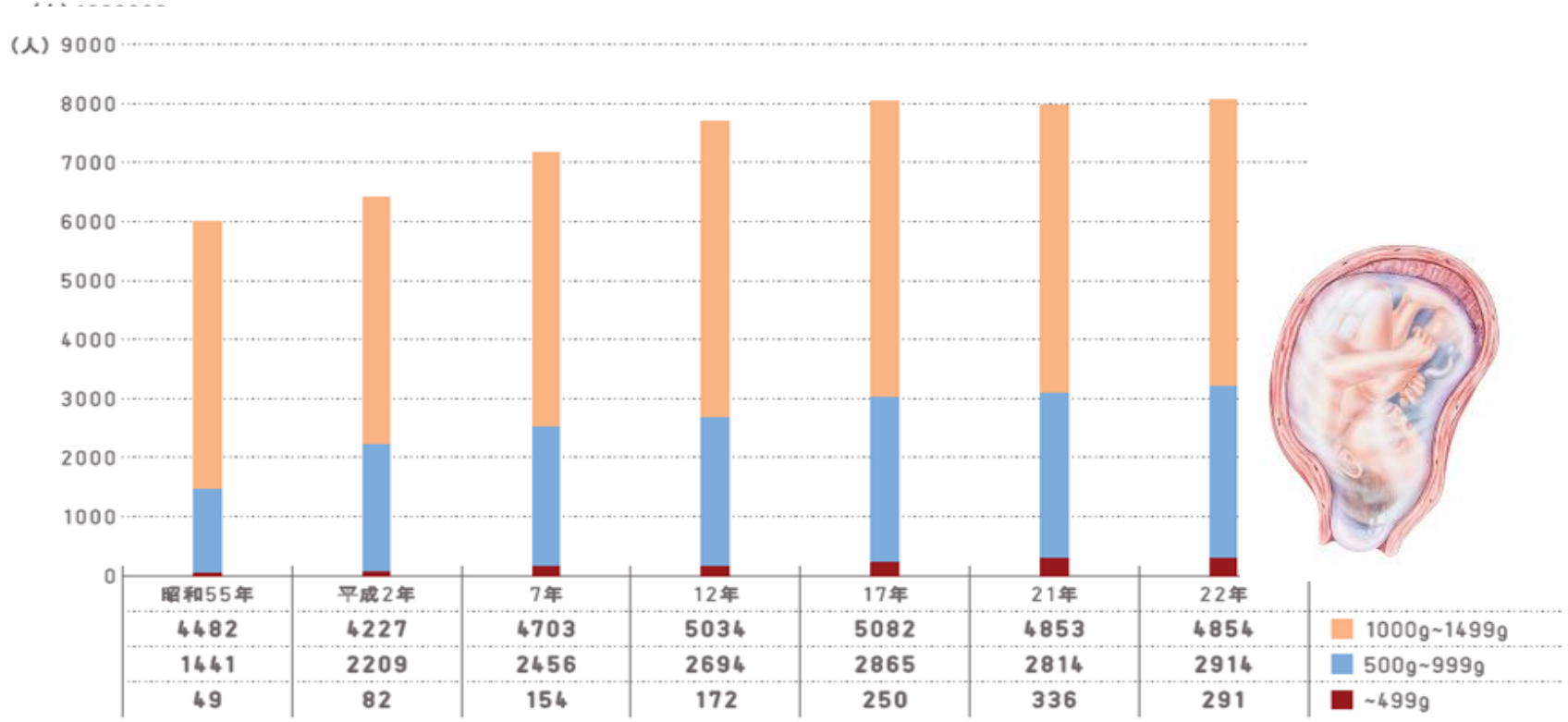
Transition of the birth weight in Japan

- Birth rate of low birth weight infant is increasing in Japan.
- Especially very-low-birth-weight(VLBW,≦1500g) infant is increasing.



Growth and development of VLBW infant

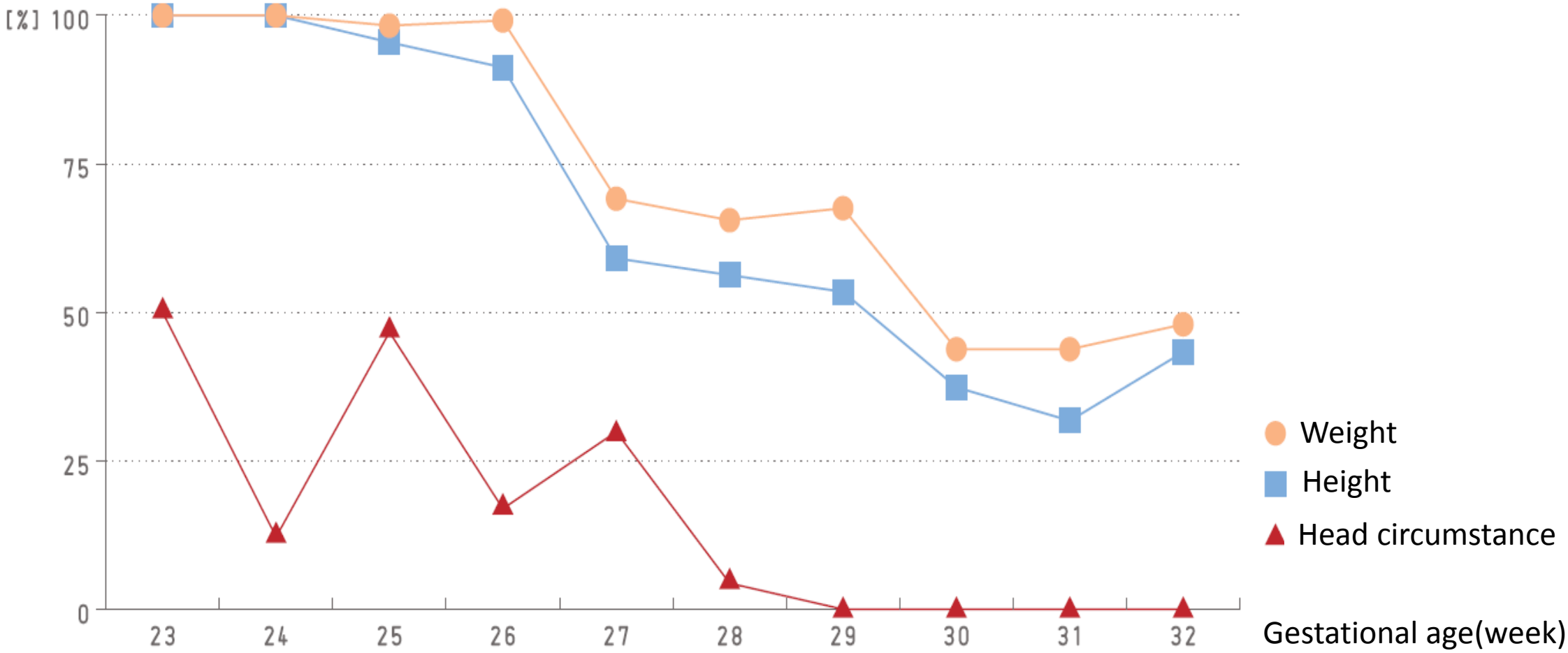
- Even each organ is immature in VLBW infant, they need enough nutrition to survive extra-uterine condition.

- Extra-uterine growth restriction (EUGR) is defined that preterm infant is below 10 percentile at 37 to 42weeks according to gestational week matched body measurement.
- Many VLBW infant experience EUGR.

Sakurai M et al ;Pediatrics international.2008

- EUGR results in growth failure and a low intelligence quotient (IQ) from school age onward.

Frequency of EUGR in Japan



Sakurai M et al;Pediatrics International.2008

Developmental Quotient at 3years old who born as very low birth weight infant

Birth Weight	＜1000g		1000～1500g	
	n	(%)	n	(%)
number of registration	2,332	100	2953	100
death	404	17.3	101	3.4
follow up data(+)	1354	58.1	1727	58.5
number who checked DQ	880	65.6	1163	67.3
DQ(71～84)	288	32.7	316	27.4
DQ＜70	183	20.8	103	8.9

※DQ: Developmental Quotient

Early aggressive nutrition

- Nutrition against VLBW infant has been changed since 2000.
- Early aggressive nutrition has been popular to prevent EUGR.
- Start efficient amount of intravenous glucose, amino acid and lipid emulsion soon after birth and enteral mother milk in a couple of day to prevent EUGR and improve the outcome of the development.

Problem of Intravenous Lipid emulsion

- Intake of lipids is required for the growth of the CNS.
- VLBW infants in whom enteral nutrition is difficult, administering intravenous lipid emulsions soon after birth is important.
- However, this treatment is only given to some VLBW infants in Japan because of the concern that the lipid emulsion will aggravate respiratory conditions and inflammation in premature infants.

【Hypothesis】

Administration of a lipid emulsion aggravates infection or inflammation?

?

IL-6　IL-8　MCP-1　TNF-α
CRP　Insulin　T-bil　D-bil

respiratory disorders,
inflammation, jaundice

Purpose of the study

To check whether the intravenous lipid emulsion against VLBW infant would lead infection or inflammation.

Methods

【Subject】 ・Very-low-birth-weight (VLBW, <1500 g) infants

・Born at <32 weeks gestational age

・Between October 2013 and October 2014 at Dokkyo Medical University Hospital

- Written informed consent for voluntary participation in the study was obtained from the parents.
- Patients were randomly allocated alternately to the group with intravenous lipid emulsion treatment or the group without intravenous lipid emulsion treatment
- Infants with congenital abnormalities and major anomalies, or who were untreatable with intravenous nutrition because of a poor general condition, or who had severe complications were excluded.

Methods
—intravenous nutrition—

- Nutrition was based on the Guidelines for Intravenous Nutrition in Japan.
- Treatment with a 20% lipid emulsion with purified soybean oil was initiated at 17-34 h after birth.
- The daily dose was increased to 1 g/kg/day, and then to a maximum dose of 1.5 g/kg/day.
- Glucose administration was started at 4-8 mg/kg/min and the dose was adjusted, based on the blood glucose level.
- Amino acid administration was started at 0.5-1.0 g/kg/day and was increased by 0.5 g/kg/day up to a maximum dose of 2.5 g/kg/day, based on the same guidelines.

Methods

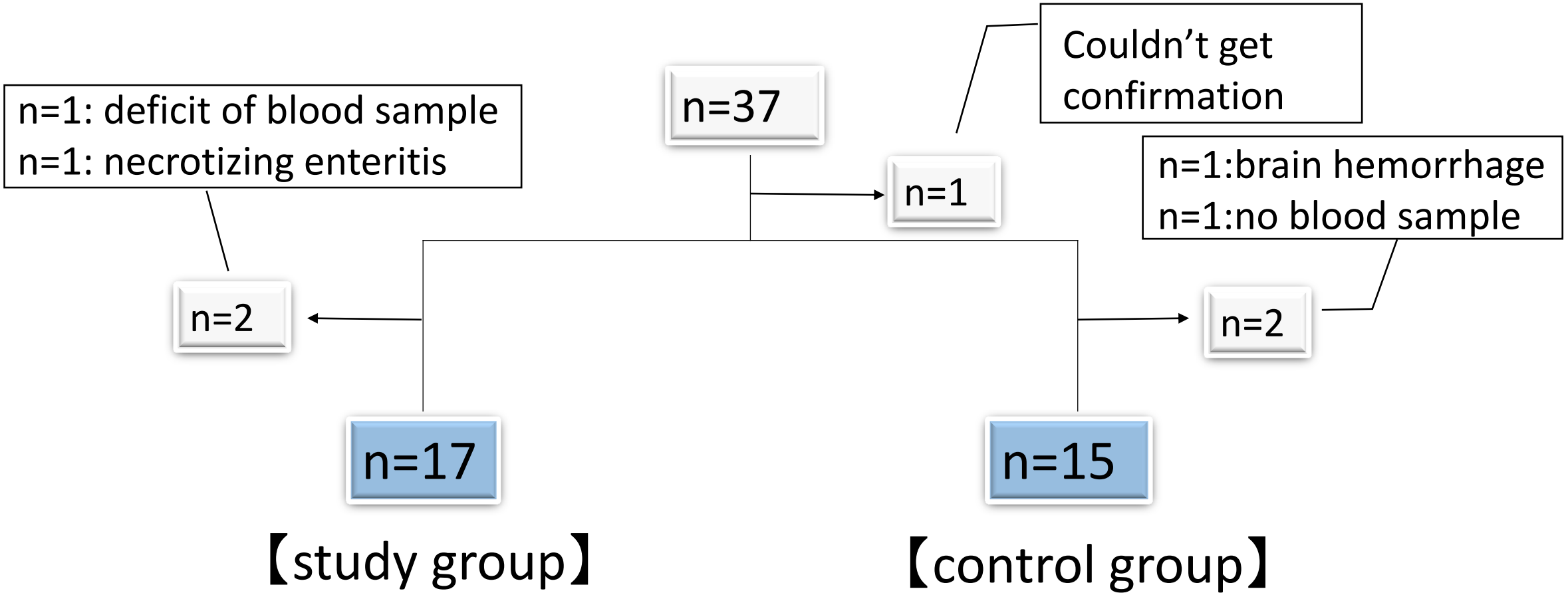
—enteral nutrition—

- Enteral nutrition was initiated within 48 h after birth with mother milk.
- Starting amount is based on 10 mL/kg/day, then began to increase over 10 mL/kg/day by a few days.

—data collection—

- Blood tests were performed before (day 1) and after (day 8) lipid administration.
- The IL-6, IL-8, MCP-1, TNFα, CRP, total bilirubin (T-Bil), direct bilirubin (D-Bil), and insulin levels were measured.
- Respirator use on days 1–10, the need for surfactant, and the mean fraction of inspired oxygen (FiO_2) on days 1, 8, and 10 were compared between the groups.

Classification of the patient



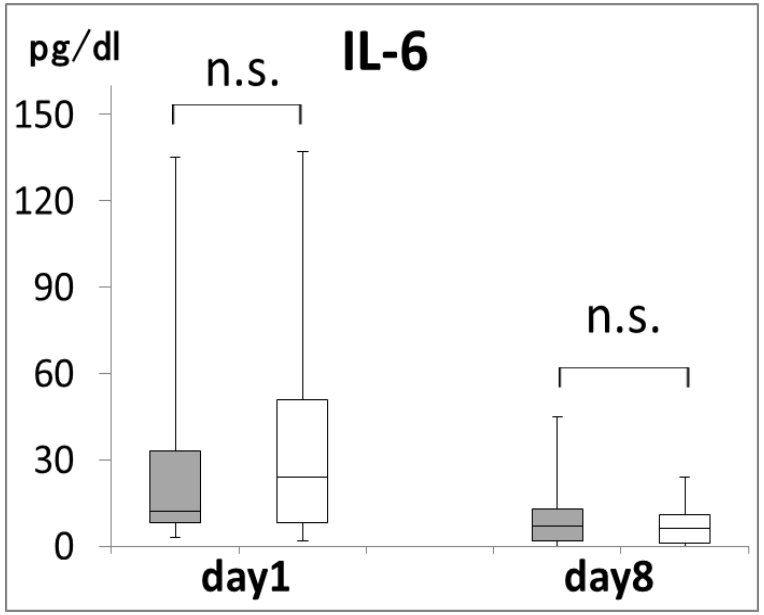
Basic data of study population

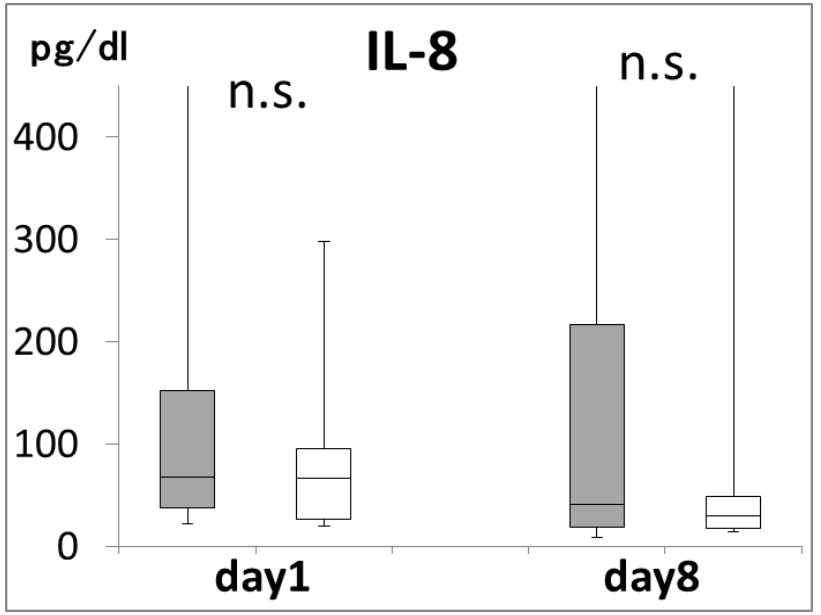
Characteristics	Study group (n=17)	Control group (n=15)	*P*
Gestational age (d)	200±10	190±21	0.062
Birth weight (g)	1018±222	848±284	0.092
Birth weight SD score	−1.03±1.11	−1.01±1.10	0.94
Birth length (cm)	34.8±2.8	33.0±3.4	0.15
Birth length SD score	−1.07±1.13	−0.76±1.10	0.25
Boys, no. (%)	11 (64.7%)	6 (40.0%)	0.28
Small for gestational age infants, no. (%)	7 (41.1%)	5 (33.3%)	0.72
Cesarean section procedures, no. (%)	12 (70.5%)	8 (53.3%)	0.46
Apgar score at 1 min	4±1	3±1	0.24
CAM grade ≥2, no. (%)	3 (17.6%)	6 (40.0%)	0.24
IgM (mg/dL) of umbilical cord blood	5±2	7±4	0.31

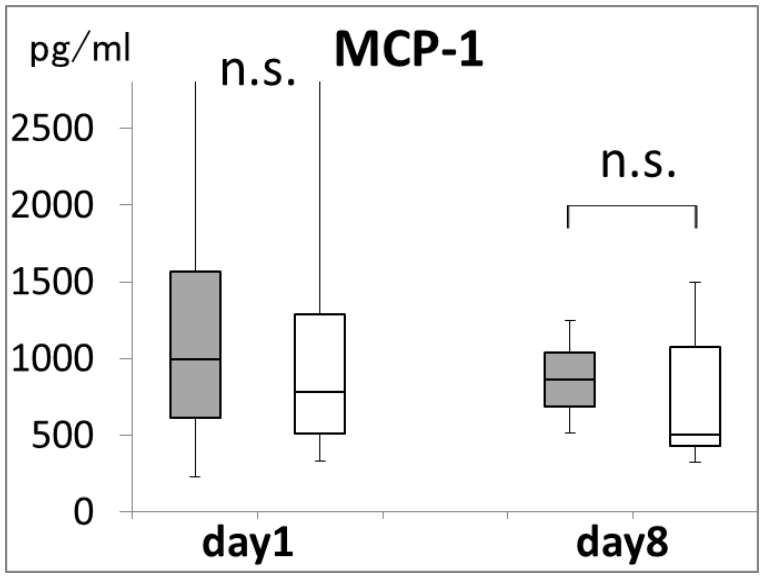
Comparison of nutrition

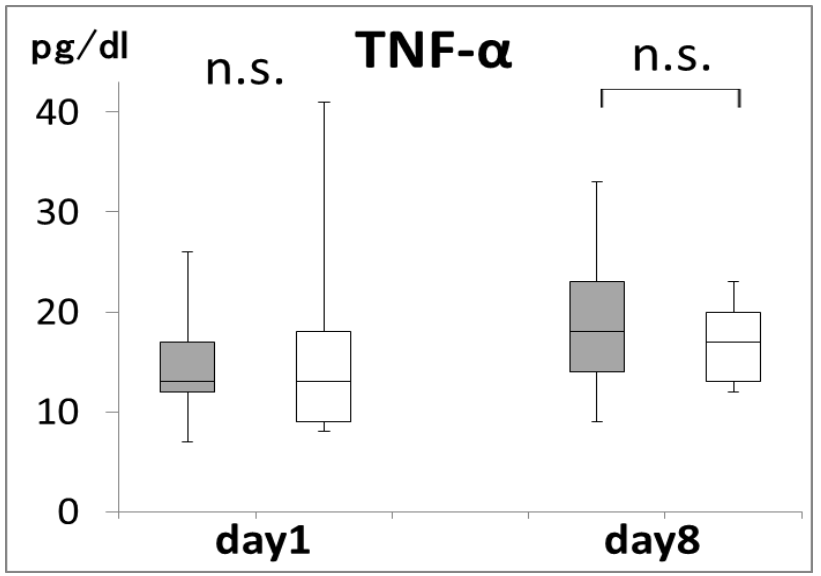
Characteristics	Study group (n=17)	Control group (n=15)	*P*
I.V. intake to 8 days after birth			
Glucose (g/kg)	53.1±15.7	48.9±17.7	0.73
Amino acids (g/kg)	10.6±3.5	8.9±5.1	0.39
Lipid (g/kg)	7.3±1.7	0	<.0001
Enteral intake to 8 days after birth			
Glucose (g/kg)	12.5±9.9	14.7±10.9	0.82
Protein (g/kg)	2.9±2.3	3.2±2.5	0.97
Lipid (g/kg)	6.8±5.2	8.4±5.6	0.57
Enteral nutrition at 8 days after birth (mL/kg/day)	65.1±34.8	62.3±40.1	0.94
Breastfeeding rates at 8 days after birth (%)	65.5±38.4	81.6±29.7	0.24

Result 【Blood test①】

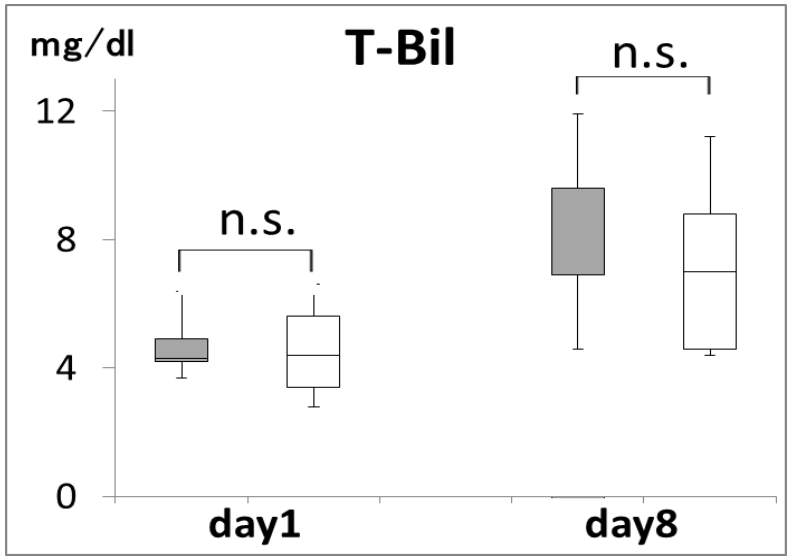


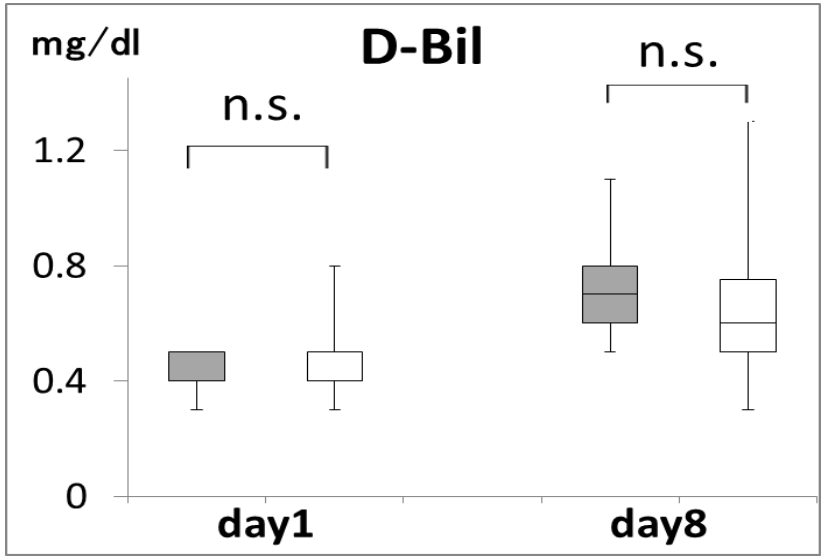


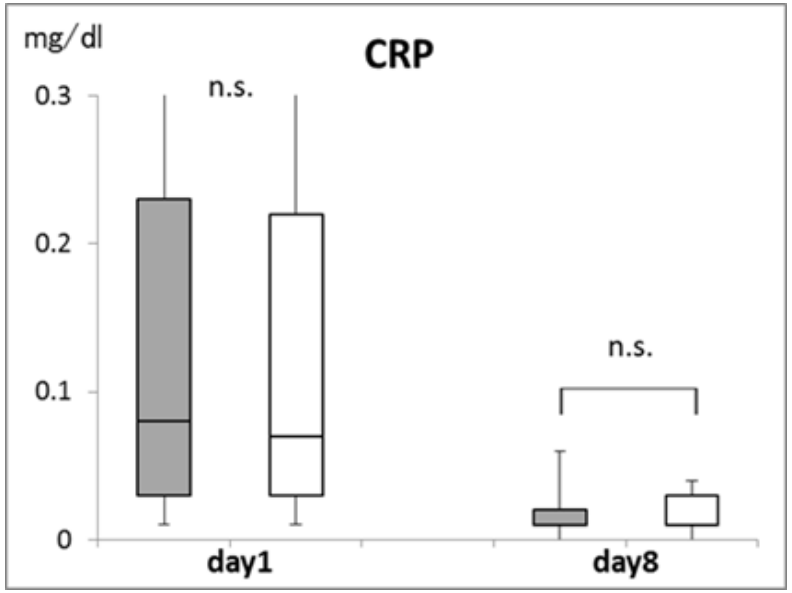


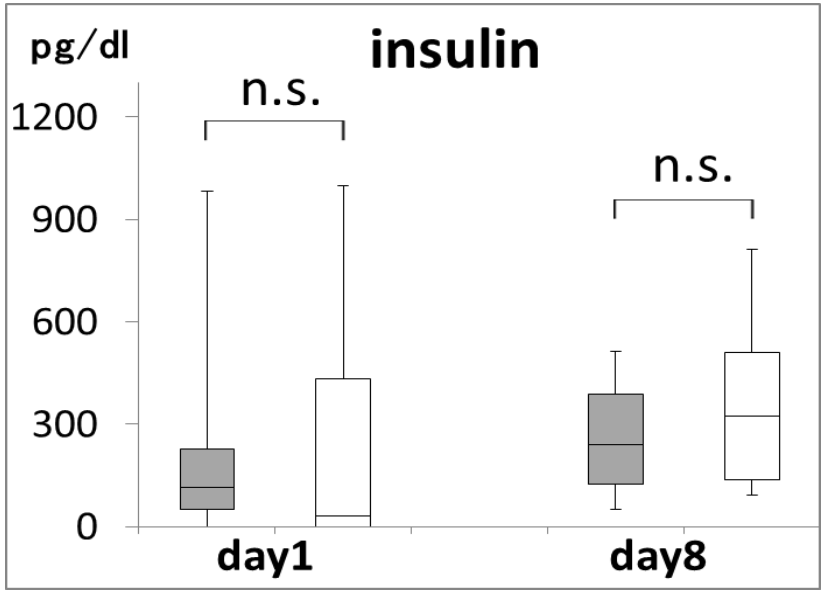


Result 【Blood test②】









study group
control group

Result 【clinical findings】

Characteristics	Study group (n=17)	Control group (n=15)	*P*
Respiratory disturbance			
Supplemental oxygen, day 1, FiO_2	0.26±0.06	0.25±0.03	0.82
Supplemental oxygen, day 8, FiO_2	0.24±0.01	0.23±0.02	0.47
Supplemental oxygen, day 10, FiO_2	0.24±0.02	0.23±0.02	0.43
Required surfactant rescue, no. (%)	5 (29.4)	6 (40.0)	0.71
Required mechanical ventilation, no. (%)	5 (29.5)	9 (60.0)	0.15
Infection			
Antibiotic therapy, no. (%) (excludes prophylactic treatment)	2 (11.7)	1 (6.6)	1.0
Duration of phototherapy (days)	1.9±0.9	1.9±0.8	0.98

Discussion①

- Effect of omega-6 polyunsaturated fatty acids against immune function, respiratory conditions and metabolic disorder

Omega-6 polyunsaturated fatty acids

- Omega-6 polyunsaturated fatty acids may affect immune function through several mechanisms, including influences on lymphocyte and macrophage functions. *Mateu-de Antonio J et al ;Br J Nutr. 2008*

- Lipid administration during the first 21 days is significantly associated with the development of chronic lung disease. *R W Cooke ;Arch Dis Child. 1991*

- Omega-6 polyunsaturated fatty acids have been implicated as a cause of cholestatic liver failure. *Prathima et al ; Adv Nutr. 2013*

- Our results showed that lipid emulsions induced no significant increases in inflammatory cytokine levels or aggravation of respiratory disorders or worsening of cholestatic jaundice in VLBW infants soon after birth.

Discussion②

- Nutrition against Very Low Birth Weight Infant

- Early aggressive nutrition

VLBW infant and early aggressive nutrition

- Aggressive nutrition started soon after birth against VLBW infant could be done safety without any side effect. *Wilson DC et al ;Arch Dis Child Fetal Neonatal Ed. 1997*

- VLBW infants who experienced severe EUGR wouldn't catch up, they should receive efficient nutrition soon after birth.

  Pampanini V et al. Eur J Pediatr.2014, Embleton ND et al ;World Rev Nutr Diet. 2014

- In one study, growth and development at 18 months old were markedly promoted in infants administered an increased amount of calories using Intralipid for 1 week after birth. *Stephens BE et al. ;Pediatrics. 2009*

● According to this study, intravenous lipid infusion started soon after birth didn’t worsen blood sample data and also clinical symptoms.

● This would allow early aggressive nutrition soon after birth and lead to better head circumference growth and results in a higher intelligence quotient (IQ) .

Discussion ③

- There are some study that the administration of fish oil to VLBW infants is safe and improves inflammation and nerve growth.

Omega-3 polyunsaturated fatty acids

- Administration of fish oil to VLBW infants is safe and improves inflammation and nerve growth. *D'Ascenzo R et al ;J Pediatr. 2011*

- Administration of omega-3 polyunsaturated fatty acids resulted in decreased level of TNF-α and IL-8 compared to administration of omega-6 polyunsaturated fatty acids. *Mayer K et al ;J Immunol. 2003*

- Administration of omega-3 polyunsaturated fatty acids resulted in decreased level of inflammatory cytokine such as IL-6 and IL-8 compared to administration of *Berger MM et al ;Am J Clin Nutr. 2013*

Conclusion

- Our results showed that lipid emulsions induced no significant increases in inflammatory cytokine levels or aggravation of infection, respiratory disorders or worsening of cholestatic jaundice in VLBW infants soon after birth.

- Establishment of the safety of lipid emulsions in these infants will allow this treatment to be administered soon after birth with the subsequent prevention of postnatal growth restriction and probable improvement of the prognosis for intellectual development.