

# Clinical Factors Affecting Lipid Metabolism and Optimal Dose of Heparin in Preterm Infants on Parenteral Nutrition

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**Purpose:** Preterm infants on parenteral nutrition are at a relatively high risk for hypertriglyceridemia because they have immature lipoprotein lipase activity. The purpose of this study was to analyze the clinical factors affecting lipid metabolism in preterm infants receiving parenteral nutrition and to evaluate the influence of intravenous heparin on serum triglycerides to determine the adequate heparin dose to prevent hypertriglyceridemia in preterm infants.

**Methods:** A single-center retrospective review was conducted among preterm infants receiving parenteral nutrition between January 2006 and February 2011. In 75 patients, 110 determinations were performed within 28 days post-natal age. Demographic and clinical data, including laboratory parameters, the dose and the duration of lipid administration, and the amount of intravenous heparin, were analyzed.

**Results:** Serum triglycerides were higher in the small for gestational age (SGA) infants than in the appropriate for gestational age infants (185.5±134.9 mg/dL vs. 126.9±101.9 mg/dL,  $p=0.019$ ). Birth weight, gestational age, and body weight were negatively correlated with serum triglyceride level ( $r=-0.289$ ,  $p=0.002$ ;  $r=-0.208$ ,  $p=0.029$ ;  $r=-0.287$ ,  $p=0.002$ , respectively). The serum triglyceride level was statistically lower in preterm infants receiving 1 U/mL of heparin than in those receiving 0.5 U/mL heparin or no heparin.

**Conclusion:** Preterm infants receiving parenteral nutrition, particularly SGA and extremely low birth weight infants, tend to have hypertriglyceridemia. Thus, administration of 1 U/mL of heparin rather than 0.5 U/mL or none may be helpful to prevent hypertriglyceridemia in preterm infants. (*Pediatr Gastroenterol Hepatol Nutr* 2013; 16: 116 ~ 122)

**Key Words:** Lipids, Hypertriglyceridemia, Parenteral nutrition, Heparin, Preterm infant

## INTRODUCTION

Lipid is an essential nutrient and important energy source, and lipid requirement is increased in

preterm infants because preterm infants require more energy to catch up on growth compared to term infants or children. Thus, sufficient energy should be supplied by administration of lipid emulsion during

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parenteral nutrition until preterm infants adapt to full enteral nutrition. However, hypertriglyceridemia frequently occurs in preterm infants because the rate of lipid clearance is decreased in preterm infants due to immature enzyme systems, limited adipose tissue mass, and hepatic immaturity [1]. Gestational age (GA), weight appropriateness for GA, postnatal age, and lipid administration dose have been proposed as possible risk factors for hypertriglyceridemia in preterm infants [2].

Lipoprotein lipase (LPL) plays a major role in the hydrolysis of absorbed fat into fatty acids [3], and various factors can affect LPL activity, including the patient's nutritional state, hormones, catecholamine, interacting proteins, and tissue factors [4]. Furthermore, LPL can be released into the circulation by the intravenous administration of heparin since LPL is anchored by an ionic interaction with heparin sulfate proteoglycans and/or by glycosyl phosphatidyl inositol [4]. However, heparin-induced LPL activity is also depressed in preterm infants [5], thus they may require different guidelines for intravenous heparin usage due to high risk for hypertriglyceridemia in this group. Nevertheless, few data has been generated up to date on the relationship between heparin dose and lipid metabolism in preterm infants.

Therefore, the aim of this study was to analyze the clinical factors affecting lipid metabolism in preterm infants receiving parenteral nutrition and to evaluate the influence of different doses of intravenously administered heparin on lipid metabolism and determine the optimal heparin dose to prevent hypertriglyceridemia in preterm infants.

## MATERIALS AND METHODS

### Study population and data collection

Preterm infants (GA < 37 weeks at birth; birth weight < 2,500 g) receiving parenteral nutrition in the neonatal intensive care unit (NICU) of Seoul National University Bundang Hospital from January 2006 to February 2011 were included. Preterm infants who were not administered lipid emulsion be-

cause of medical conditions such as sepsis or advanced enteral feeding, and had imminent life threatening congenital anomaly were excluded.

Preterm infants were classified into extremely low birth weight (ELBW) infants (birth weight < 1,000 g), very low birth weight (VLBW) infants (birth weight < 1,500 g), and low birth weight (LBW) infants (birth weight < 2,500 g). In addition, preterm infants were also classified into appropriate for gestational age (AGA) infants and small for gestational age (SGA) infants according to the appropriateness of birth weight for GA.

The demographic and clinical data of each patient were analyzed retrospectively. These data included GA, gender, birth weight, appropriateness of birth weight for GA, postnatal age, body weight at the determination of laboratory tests, serum concentrations of triglyceride (TG) and other laboratory parameters, dose and duration of lipid administration, dose of intravenous heparin, presence of significant bleeding, and history of percutaneous central venous catheter (PCVC) obstruction.

Intravenous lipid emulsion was administered to all subjects along with parenteral nutrition using 20% LipoMCT (a mixture of purified soybean oil and medium chain TG), usually starting from the second day of life. The amount of lipid was started at 0.5-1 g/kg and was increased gradually up to the final amount (maximum lipid amount, 4 g/kg/day). Intravenous lipid was continuously infused using an infusion pump with light protection.

The prescription and preparation of parenteral nutritional solution and lipid emulsion were supervised and monitored daily by the pediatric nutritional support team of the NICU according to the clinical status and nutritional requirement of each patient. The pediatric nutritional support team of our hospital is composed of pediatric gastroenterologists, neonatologists, pediatric dieticians, pediatric pharmacists, and NICU nurses in order to provide a multidisciplinary approach for optimal nutritional support.

Intravenous heparin was administered at a dose of 0 U/mL, 0.5 U/mL, or 1 U/mL during parenteral

nutrition. It was added into total parenteral nutrition infusates and the dose of heparin was assigned randomly. Intravenous heparin was not administered if the patient had a risk of bleeding, such as thrombocytopenia, coagulopathy, or fluctuating blood pressure.

Lipid infusion was monitored using serum TG level. It was checked within 3 to 7 days from birthday or changes of the dose of lipid. Hypertriglyceridemia was defined as a serum TG level greater than 150 mg/dL. Laboratory parameters, including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total cholesterol, and ionized calcium levels, were also checked.

### Statistics

Data are presented as mean±standard deviation for parametric data and median with interquartile range for nonparametric data. The Student t-test was used to compare the hypertriglyceridemia group and the normal-TG group. Correlations between serum TG level and other parameters were calculated by Pearson’s correlation analysis. Patients were categorized into subgroups based on the dose of heparin, and serum TG levels in each subgroup were analyzed using the Kruskal-Wallis test. SPSS version 18.0 was used (SPSS Inc., Chicago, IL, USA). Statistical significance was accepted at a *p*-value <0.05.

### Ethics

This study was approved by the Institutional

Review Board of Seoul National University Bundang Hospital.

## RESULTS

### Patient characteristics

During the study period, 110 laboratory determinations within 28 days postnatal age in 75 infants (39 boys and 36 girls) were retrospectively eligible. Recruited infants and their allocations are shown in Fig. 1.

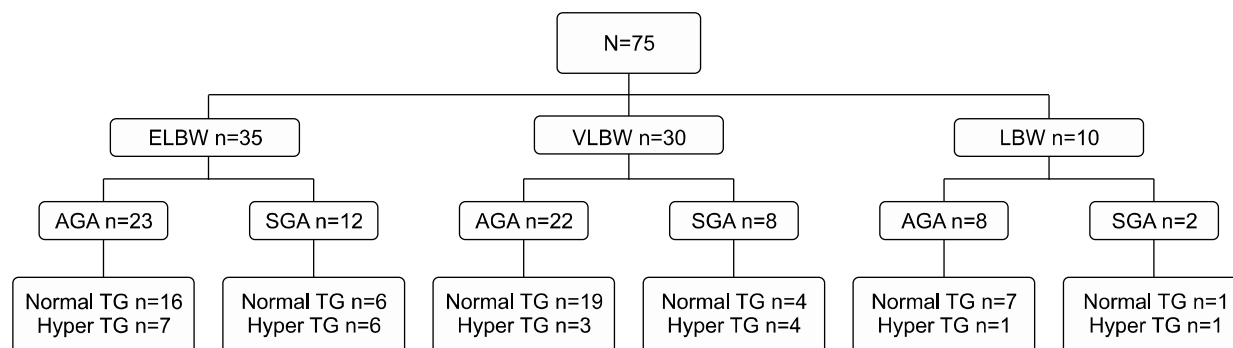
### Hypertriglyceridemia according to birth weight and other clinical features

Among ELBW and AGA infants, 7 of 23 had serum TG levels exceeding 150 mg/dL (30.4%). Among ELBW and SGA infants, 6 of 12 had serum TG levels indicative of hypertriglyceridemia (50%). Hypertriglyceridemia was also frequent in SGA infants of the VLBW and LBW groups.

In total, 30 of 110 determinations showed hypertriglyceridemia. The demographic features and clinical parameters were compared between the normal-TG and the hypertriglyceridemia groups (Table 1). The gender ratio was significantly different between the 2 groups, with a male predominance in the hypertriglyceridemia group.

### The relationship between serum triglyceride levels and clinical parameters

The serum TG levels were higher in SGA infants



**Fig. 1.** Flowchart of patient recruitment and allocation. ELBW: extremely low birth weight, VLBW: very low birth weight, LBW: low birth weight, AGA: appropriate for gestational age, SGA: small for gestational age, TG: triglyceride.

**Table 1.** Demographic and Clinical Data of the Subjects Divided into 2 Groups Based on Serum Triglyceride Levels

Factors	Normal TG (n=80)	Hyper TG (n=30)	p-value
Neonatal factors			
Gender (male : female)	37 : 43 (male: 46%)	21 : 9 (male: 70%)	0.033*
SGA : AGA	24 : 56 (SGA: 30%)	17 : 13 (SGA: 57%)	0.015*
GA, mean (week)	28.6±2.9	28.2±3.3	0.562
Birth weight, mean (g)	1,043±392	897±347	0.077
ELBW proportion	44 (55%)	18 (60%)	0.67
Factors related to lipid infusion (mean)			
Total lipid amount (g/kg/day)	3.1±0.9	3.2±0.8	0.730
Infused lipid amount (g/kg/day)	2.5±0.9	2.7±0.7	0.339
Duration of lipid infusion (day)	9.6±7.3	10.2±8.4	0.708
Infused heparin amount (U/mL)	0.40±0.41	0.30±0.32	0.160
Body weight (kg)	1.08±0.42	0.91±0.35	0.062
Laboratory parameters (mean)			
Cholesterol (mg/dL)	118±41	133±33	0.087
AST (IU/L)	31±28	26±10	0.303
ALT (IU/L)	10±13	11±12	0.664
Total bilirubin (mg/dL)	6.5±5.1	4.7±2.7	0.083
Ionized calcium (mmol/L)	1.35±0.15	1.30±0.24	0.298

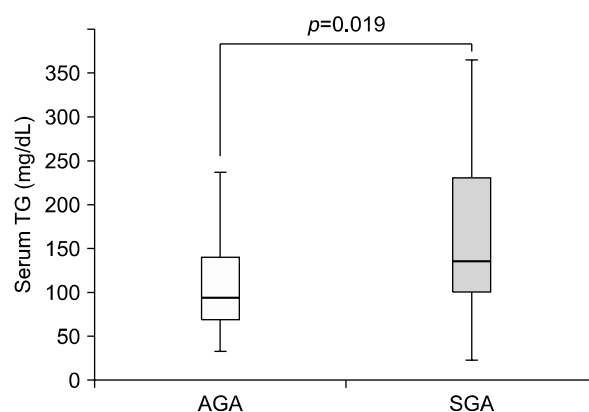
Values are presented as number (%) or mean±standard deviation. TG: triglyceride, SGA: small for gestational age, AGA: appropriate for gestational age, GA: gestational age, ELBW: extremely low birth weight, AST: aspartate aminotransferase, ALT: alanine aminotransferase. \* $p < 0.05$ .

than in AGA infants ( $185.5 \pm 134.9$  mg/dL vs.  $126.9 \pm 101.9$  mg/dL,  $p = 0.019$ ) (Fig. 2). Other clinical and laboratory parameters as well as disease severity, morbidity, and respiratory status were not different between the normal-TG and the hypertriglyceridemia groups (Table 1).

Among clinical parameters, birth weight, GA, and body weight were negatively correlated with serum TG level ( $r = -0.289$ ,  $p = 0.002$ ;  $r = -0.208$ ,  $p = 0.029$ ;  $r = -0.287$ ,  $p = 0.002$ , respectively), and postnatal age was not significantly correlated with serum TG ( $r = 0.104$ ,  $p = 0.280$ ). The dose of administered lipid was not correlated with serum TG ( $r = 0.062$ ,  $p = 0.516$ ).

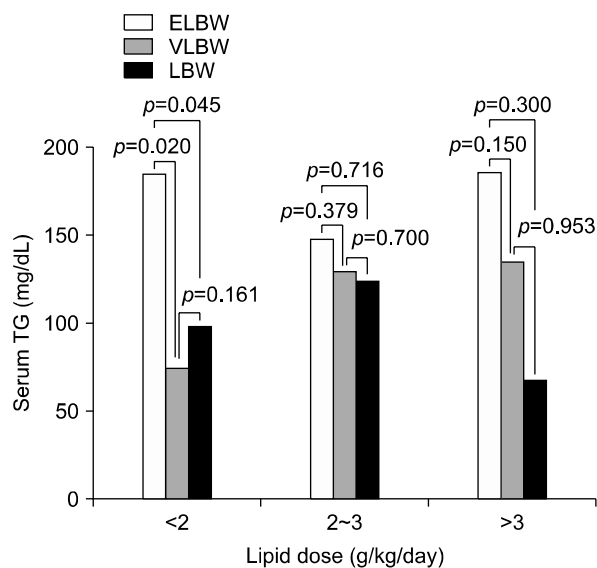
### The relationship between serum triglyceride levels and the dose of lipid

Serum TG levels were higher in ELBW infants than in the other 2 birth weight groups, regardless of the amount of administered lipid ( $172.6 \pm 137.1$  mg/dL in ELBW vs.  $119.0 \pm 84.8$  mg/dL in VLBW vs.  $147.9 \pm 124.1$  mg/dL in LBW,  $p = 0.032$ ). When serum TG levels were compared according to the dose of ad-



**Fig. 2.** Comparison of serum triglyceride (TG) levels between appropriate for gestational age (AGA) and small for gestational age (SGA) infants. The mean serum TG levels were  $126.9 \pm 101.9$  mg/dL in AGA and  $185.5 \pm 134.9$  mg/dL in SGA infants ( $p = 0.019$ ).

ministered lipid among the 3 birth weight groups, serum TG levels in ELBW infants receiving lipid less than 2 g/kg/day were significantly higher than those in the other 2 birth weight groups receiving the same dose of lipid ( $p = 0.045$ ) (Fig. 3).

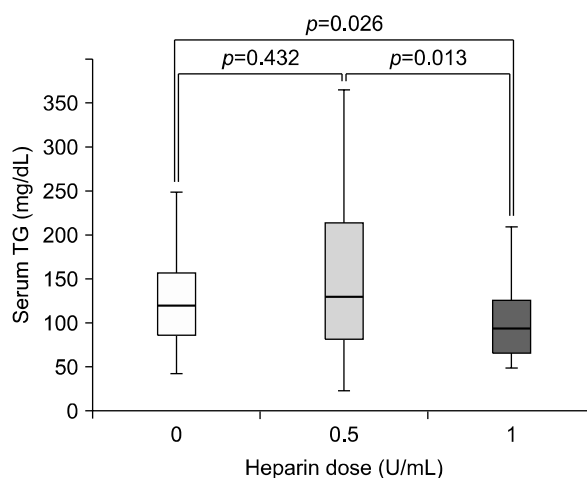


**Fig. 3.** Trend of serum triglyceride (TG) levels based on lipid administration. Serum TG levels were higher in extremely low birth weight (ELBW) infants than in the other 2 groups, especially with low dose lipid (<2 g/kg/day). VLBW: very low birth weight, LBW: low birth weight.

### Influence of heparin doses on serum triglyceride levels in preterm infants

When the patients were categorized into 3 groups according to the amount of intravenous heparin, the median serum TG levels were 120 mg/dL (range: 42-600 mg/dL) with no heparin, 130 mg/dL (range: 2-576 mg/dL) with 0.5 U/mL of heparin, and 94 mg/dL (range: 49-351 mg/dL) with 1 U/mL heparin. The serum TG level was statistically lower in preterm infants receiving 1 U/mL heparin than in those receiving 0.5 U/mL heparin or no heparin. No significant difference in serum TG was observed between the 0 and 0.5 U/mL heparin groups (Fig. 4).

Birth weight, GA, body weight, male proportion, the presence or absence of respiratory distress syndrome which reflects the demand of FIO<sub>2</sub>, and other treatment such as steroids administration before and after birth, antibiotics, immunoglobulin, and catecholamines had no significant difference. No significant bleeding such as intracranial hemorrhage, pulmonary hemorrhage, or gastrointestinal hemorrhage occurred during heparin administration related to parenteral nutrition. Further-



**Fig. 4.** Serum triglyceride (TG) levels among the 3 groups based on the amount of heparin: medians and interquartile range. The serum TG concentration was significantly lower in the 1 U/mL heparin group than in the 0.5 U/mL group or the no heparin group. The serum TG levels were not significantly different in the 0.5 U/mL heparin and no heparin groups.

more, the frequency of PCVC exchange caused by catheter obstruction was not significantly different between the heparin infusion group and the no heparin group ( $p > 0.05$ ).

### DISCUSSION

Because premature infants cannot proceed to full enteral nutrition immediately after birth, lipid emulsion is their most important concentrated source of energy and essential fatty acids. Providing sufficient lipids to premature infants is beneficial to meet their nutritional requirements for growth [6]. However, premature infants have low LPL levels, little adipose tissue mass, and low tissue levels of carnitine; these can be major causes of hypertriglyceridemia and risk factors for metabolic disease, especially in preterm infants [7,8]. Although the consequences of hypertriglyceridemia in early life have not been clearly established, hypertriglyceridemia can cause decreased arterial oxygenation by decreasing pulmonary diffusion capacity and deposition of lipid particles in pulmonary capillaries, resulting impaired immune function and increased risk of infection [3].

Hypertriglyceridemia also can affect the results of biochemical tests and can displace unconjugated bilirubin, possibly increasing the risk of hyperbilirubinemia and kernicterus [3].

Because of clinical significance of hypertriglyceridemia that occurs in preterm infants, various clinical factors were evaluated as potential risk factors affecting lipid metabolism in the present study. Twenty-two of 75 (29%) premature infants had high serum TG levels indicative of hypertriglyceridemia during the study period, and this was more frequent in ELBW (37%) than in VLBW (23%) or LBW (20%) infants. Hypertriglyceridemia was also more common in SGA than in AGA infants. Furthermore, birth weight and GA were negatively correlated with serum TG levels in our study. These results are consistent with previous studies reporting that body weight and relative birth weight may affect LPL activity [9]. Maturation of lipid metabolism was associated with weight gain rather than aging because body weight, but not postnatal age, showed a negative correlation with serum TG levels.

When we compared liver function, renal function, and clearance of cholesterol between the 2 groups based on the presence of hypertriglyceridemia, no differences were observed in serum AST, ALT, total bilirubin, blood urea nitrogen, creatinine, and cholesterol levels. The serum calcium level, which can trigger the folding of LPL into active dimers [10], was also not different between the 2 groups in our study.

In our study, there was a male predominance in the hypertriglyceridemia group. Although female sex hormone concentrations do not influence lipolysis and fatty acid availability, a previous study in adults showed that very low density lipoprotein-TG can be removed more efficiently in women than in men [11]. Because there is no data in infants, further investigations may be required in a large study group.

Regarding the dose of infused lipid, Drenckpohl et al. [12] compared low-dose versus high-dose intravenous lipids in preterm infants; serum TG levels were significantly higher in the high-dose lipid group than in the low-dose lipid group, but the high-dose lipid group did not have more hyper-

triglyceridemia, and serum TG levels increased in proportion to increased lipid infusion. In contrast, in our study, serum TG levels did not correlate with the amount of infused lipids directly, and the amount of infused lipid as a single factor did not significantly increase serum TG levels in either the normal-TG groups or in the hypertriglyceridemia group. Serum TG levels were higher in ELBW infants than in the other birth weight groups in our study, even with low-dose lipid (<2 g/kg/day) administration, indicating that birth weight is a more important risk factor for high serum TG levels in preterm infants than the infused lipid dose. The patients without heparin administration indicated less proportion of ELBW (37%) and higher TG levels compared with the other two groups (51%, 67%, respectively); thus birth weight might also be an influential factor. Therefore, ELBW infants require special attention and regular serum TG level monitoring from the initiation of parenteral nutrition because this birth weight group is at risk of hypertriglyceridemia.

It is well known that heparin administration can activate LPL and release hepatic lipase [13,14]. Thus, routine administration of intravenous heparin along with parenteral nutrition and lipid infusion is required in premature infants. However, there is no consensus on the appropriate dose of heparin that should be infused with parenteral nutrition solution yet.

A recent meta-analysis reported that the effect of heparin administered through an intravenous catheter could not be determined because of insufficient data on the effectiveness, optimal dose, and safety of heparin for intravenous catheter use in neonates [15], and Silvers et al. [16] suggested that lipid metabolism may be facilitated with low dose heparin and reported increased viscosity after heparin administration. However, in our study, administration of 1 U/mL of intravenous heparin decreased serum TG levels more efficiently than 0.5 U/mL of heparin. Notably, 0.5 U/mL of heparin did not significantly change serum TG levels compared to the no heparin group. Additionally, no significant complications occurred with heparin administration in our study regardless of heparin dose. TG-lowering

effect of high dose heparin is meaningful especially in the patients at high risk for hypertriglyceridemia. Therefore, administering 1 U/mL of heparin may be helpful in preventing hypertriglyceridemia in preterm infants receiving parenteral nutrition.

In summary, preterm infants, especially SGA or ELBW infants, are at a high risk of hypertriglyceridemia even with low dose lipid infusion because they require more lipid for growth and their LPL activity is relatively immature. Because increased serum TG levels can affect the clinical status of preterm infants, serum TG levels should be carefully monitored and hypertriglyceridemia should be prevented in these high risk groups. Intravenous administration of 1 U/mL heparin along with parenteral nutrition might help to prevent hypertriglyceridemia in preterm infants, especially in ELBW infants.

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