Parenteral Soybean Oil Lipid Emulsion in Very Low Birth Weight (VLBW) in Intensive Care

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Hiromichi Shoji and Toshiaki Shimizu

Contents

Abstract

Preterm infants, especially very low birth weight (VLBW) infants, often require parenteral lipid emulsion (LE) if adequate energy and lipid intake cannot be achieved by enteral feeding. This is because their polyunsaturated fatty acid (PUFA) body stores are very low, whereas their metabolic requirements are high. The conventional LE for preterm infants is mostly soybean oil. However, the adequacy of soybean LE has been questioned, primarily in view of the very high concentrations of linoleic acid (LA, 18:2n-6) relative to α-linolenic acid (ALA, 18:3n-3) and because of the absence of arachidonic acid (ARA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3). The large amounts of LA in soybean LE may further impair PUFA formation via substrate inhibition. A randomized controlled trial concluded that VLBW infants can tolerate 2 g/kg/day of soybean LE during the first few days of life without significant adverse events. A recent meta-analysis in preterm infants showed that parenteral LE within the first 2 days of life seems safe and well tolerated. However, larger studies are needed to confirm the effect of early LE or the results from LE in terms of growth, respiratory morbidity, and neurodevelopment for VLBW infants' short- and long-term outcomes.

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List of Abbreviations

ALA	α-Linolenic acid
ARA	Arachidonic acid
CLD	Chronic lung disease
DHA	Docosahexaenoic acid
EFA	Essential fatty acid
IVH	Intraventricular hemorrhage
LA	Linoleic acid
LCPUFA	Long-chain polyunsaturated fatty acid
LE	Lipid emulsion
MCT	Medium-chain triglyceride
NEC	Necrotizing enterocolitis
OS	Oxidative stress
PN	Parenteral nutrition
PUFA	Polyunsaturated fatty acid
ROP	Retinopathy of prematurity
VLBW	Very low birth weight

Introduction

There is growing evidence that nutrient deprivation during fetal life and early infancy has short- and long-term consequences for health and well-being. Preterm infants, especially very low birth weight (VLBW) infants (birth weight <1,500 g), often require parenteral lipid emulsion (LE) if adequate energy and lipid intake cannot be achieved by enteral feeding. This is because their fatty acid body stores are very low due to the early termination of maternal-to-fetal fatty acid transfer (Koletzko et al. 2001). More than 90 % of adipose deposition in the fetus occurs in the last 10 weeks of gestation (Haggarty 2004).

In addition to providing an energy source, LEs supply essential fatty acids (EFAs) required for growth and development of the fetus and infant. The parent EFAs, linoleic acid (LA, 18:2n-6), and α-linolenic acid (ALA, 18:3n-3) cannot be synthesized in the human body and are therefore indispensable components of the human diet. Both LA and ALA may be converted by chain elongation, desaturation, and chain shortening into their respective long-chain metabolites, collectively named long-chain polyunsaturated fatty acids (LCPUFAs, ≥20 carbon atoms and ≥3 double bonds) (Fig. 1). Two series of n-3 and n-6 LCPUFA compete for the same enzymes and are precursors of prostaglandins, thromboxanes, and leukotrienes. Due to the interaction between both series of fatty acids, an appropriate diet consists of an optimal ratio of n-3 and n-6 fatty acids. Two LCPUFAs, docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (ARA, 20:4n-6), are the major LCPUFA components of membrane lipids in the brain and retina (Fleith and Clandinin 2005), making them essential components of infant nutrition. About 80 % of intrauterine DHA and ARA accumulation occurs during the last 3 months of pregnancy (Fleith and Clandinin 2005). Analysis of fetal autopsy tissue yielded the following estimates of intrauterine accretion of LCPUFAs during the last trimester: 106 mg/kg/day for LA, 4 mg/kg/day for ALA, 212 mg/kg/day for ARA, and 43 mg/kg/day for DHA (Lapillonne and Jensen 2009).

Preterm infants are capable of de novo synthesis of DHA and ARA from LA and ALA (Carnielli et al. 1996a; Sauerwald et al. 1996; Uauy et al. 2000; Szitanyi et al. 1999). The fetal brain is able to convert LA and ALA into LCPUFAs, but its capacity is limited and increases with gestational age (Clandinin 1999). However, it is unclear whether the de novo synthesis is sufficient to meet their physiological requirements. VLBW infants are particularly susceptible to postnatal growth failure and nutrient deficiencies. Failure to accumulate sufficient DHA may impair neurological development (Simmer and Patole 2004; SanGiovanni et al. 2000), and clinical evidence supports a relationship between blood ARA levels and infant growth (Carlson et al. 1993; Koletzko and Braun 1991). Therefore, EFA or LCPUFA supply for VLBW infants is of critical importance.

Since the 1960s, safe commercial parenteral LEs have been widely used. Soybean oil-based emulsions were the first LEs available for parenteral use and are still the most often used parenteral lipid source (Waitzberg 2005). Soybean-based LEs have been used in parenteral nutrition formulations for VLBW infants, but the adequacy of soybean LEs has been questioned, primarily in view of the very high concentrations of LA relative to ALA and the absences of ARA

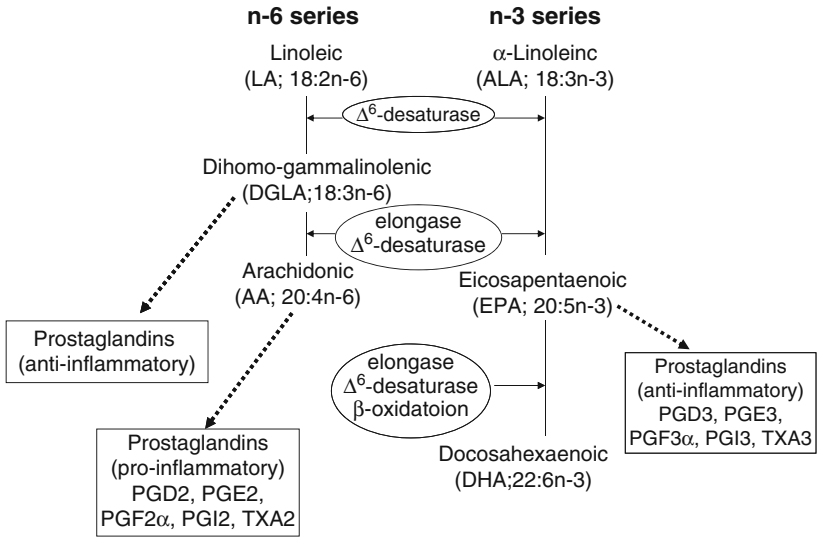

Fig. 1 Essential fatty acid pathways. *PG* prostaglandin, *TX* thromboxane

Table 1 Composition of selected lipid emulsions

	Intralipid (Fresenius Kabi)	Intralipos (Otsuka Pharmaceutical)	ClinOleic (Baxter)	SMOFlipid (Fresenius Kabi)	Omegaven (Fresenius Kabi)
Oil source (%)					
Soybean	100	100	20	30	–
Coconut (MCT)	–	–	–	30	–
Olive	–	–	80	25	–
Fish	–	–	–	15	100
Composition of major fatty acids (wt %)					
MCTs	–	–	–	29.2	–
n-6 PUFA					
Linoleic acid (18:2n-6)	53	53	19	19	4
Arachidonic (20:4n-6)	–	–	0.5	0.5	2
n-3 PUFA					
a-Linolenic acid (18:3n-3)	8	7	2	2	2
EPA (20:5n-3)	–	–	–	3	19
DHA (22:6n-3)	–	–	0.5	2	12

and n-3 PUFA (e.g., DHA and EPA) in most commercial preparations (Table 1). The n-6 PUFAs (e.g., LA and ARA) possess immunosuppressive properties, whereas ARA is a precursor of proinflammatory eicosanoids (e.g., prostaglandin E2, leukotrienes B4 and C4, thromboxane A2, and platelet aggregation factor) and can induce coagulation and production of proinflammatory cytokines (e.g., tumor necrosis factor-α and interleukin-6) (Hayashi et al. 1998; Wachtler et al. 1997; Deshpande and Simmer 2011) that contribute to lipid emulsion-associated complications. Furthermore, soybean LEs in VLBW infants are limited by concerns regarding impaired lipid

tolerance, including increased albumin-bound bilirubin displacement, increase in pulmonary vascular resistance, impaired pulmonary gas exchange, sepsis, and oxidative stress (OS) (Krohn and Koletzko 2006).

The purpose of this article was to review recent information regarding the role of parenteral soybean oil LE in VLBW.

Applications to Critical or Intensive Care

VLBW infants are usually treated routinely with total parenteral nutrition (PN) containing carbohydrates, amino acids, LEs, vitamins, and minerals to maintain their nutritional status with the aim of matching normal intrauterine growth during the first few weeks of life. In these infants, full enteral feedings are generally delayed because of the severity of medical problems associated with prematurity.

LEs are necessary in preterm infants receiving PN, because LEs have a high caloric value, low osmolarity, and EFA content (Colomb et al. 2000). Small amounts of EFA (approximately 4 % of caloric intake or 0.5 g/kg/day) are required to prevent EFA deficiency. Without supplementation, clinical manifestations of fatty acid deficiency (e.g., dermatitis, thrombocytopenia, and increased likelihood of infection and failure to thrive) become apparent by the end of the first week after birth. However, the endogenous synthesis of LCPUFA from precursor EFA is limited in preterm infants (Szitanyi et al. 1999), and the large amounts of LA and ALA in soybean oil emulsions may further impair LCPUFA formation via substrate inhibition (Koletzko et al. 1998; Rubin et al. 1994).

Shoji et al. (2011) investigated the relationship between blood DHA and ARA status in 27 VLBW infants, some of which received soybean LE. The fatty acid composition of the erythrocyte membrane was analyzed at birth and at 2 weeks of age. No significant difference in ARA levels was observed in the LE group between the two time points, whereas the ARA levels at 2 weeks were significantly lower than at birth in the control (no LE) group. The DHA levels in both groups (infants that received soybean LEs and infants that did not) at 2 weeks were significantly lower than at birth, but no group differences were observed at either time point (Fig. 2). As with previous studies of Carnielli et al. (1996b) and Koletzko et al. (2003), these results indicated that the levels of DHA and n-3 PUFA during the first 2 weeks decreased regardless of whether or not LE was administered. Therefore, the use of parenteral soybean oil LEs in VLBW infants in the postnatal period may prevent the decline in the ARA level but does not appear to influence the DHA level.

VLBW infants have only limited muscle and fat mass and thus have decreased hydrolytic capacity of the enzyme, lipoprotein lipase. As a consequence, they are at higher risk for PN-associated hypertriglyceridemia when compared with term infants (Koletzko et al. 2005). Triglyceride concentrations are highest in the first week after birth for any given lipid dose (Periera et al. 1980). A randomized controlled trial by Drenckpohl et al. (2008) showed that the introduction of 2.0 g/kg/day compared with 0.5 g/kg/day of soybean oil LE in combination with 3 g/kg/day amino acids on day 1 to VLBW infants ($n = 48$ and 52, respectively) improved energy intake, attenuated weight loss, and allowed an earlier regain of birth weight without a significant difference in the incidence of hypertriglyceridemia (defined as >200 mg/dl). They concluded that VLBW infants can tolerate 2 g/kg/day of LE during the first few days of life without significant adverse events.

Increased dietary intake of PUFA may increase the susceptibility to OS because of the chemical reactivity of the multiple doubles between carbon atoms (C=C) in the molecules. Premature infants are less prepared to cope with the oxygen-rich environment of extrauterine life, as their antioxidant mechanisms are underdeveloped when compared with infants born at term (O'Donovan and Fernandes 2004; Frank and Groseclose 1984). Indeed, OS may mediate serious diseases in premature infants, including necrotizing enterocolitis (NEC) (Aydemir et al. 2011), chronic lung disease (CLD) (Saugstad 1998; Kelly 1993), retinopathy of prematurity (ROP) (Kelly 1993), and

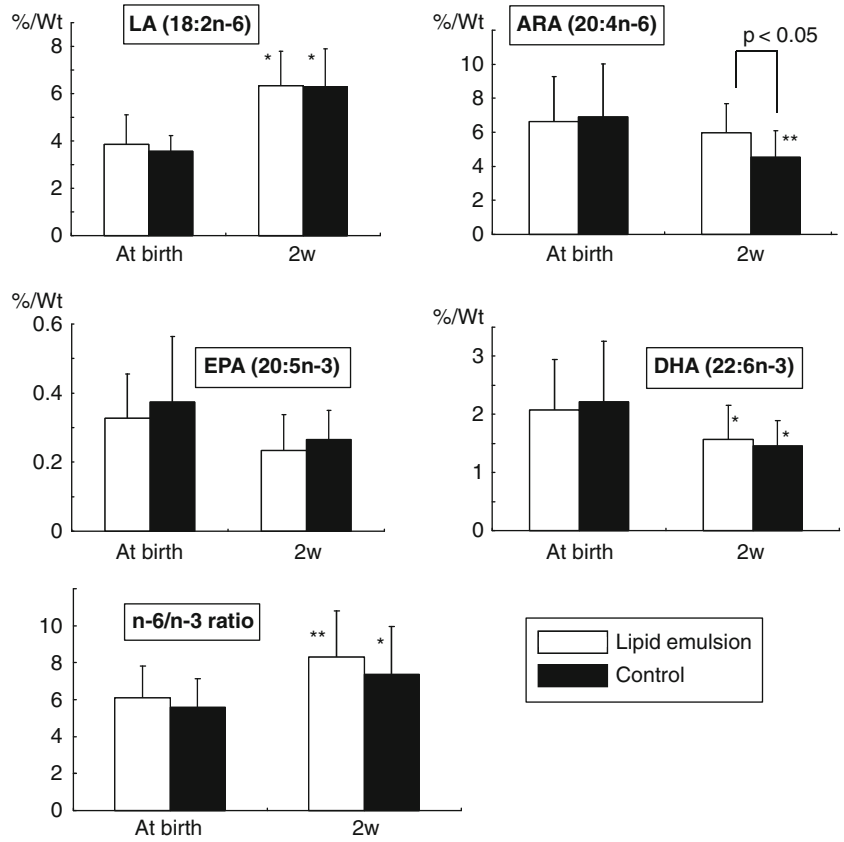

Fig. 2 Changes in the fatty acid composition of erythrocytes during the early postnatal period. Values are means + standard deviation. *p <0.05; **p <0.01 compared with the value at birth

intraventricular hemorrhage (IVH) (Kelly 1993). The morbidities associated with prematurity have been linked to OS and free radical-mediated cell and tissue injury (O'Donovan and Fernandes 2004; Saugstad 2001). LEs contain different amounts of PUFAs, which can act as substrates for the formation of lipid hydroperoxides, mediated by free radicals that lead to OS in critically ill infants. Lipid peroxidation may enhance damage of cellular membranes. The idea of LCPUFA being dangerous is supported by in vitro studies of lipid peroxidation, but in vivo systems are more complicated and are influenced by additional factors.

Göbel et al. (2003) investigated lipid peroxidation levels in preterm infants of 28–36 weeks' gestation in which one group of infants ($n = 15$) received a new LE based on olive and soybean oils (ClinOleic, Table 1) and in which another group of infants ($n = 18$) received a lipid emulsion based on soybean oil LE for 7 days. There were no group differences in urinary markers of lipid peroxidation excretion when comparing the two groups. This study indicated that the difference of PUFA quantity in fat emulsion did not affect the level of lipid peroxidation in premature infants. Shimizu et al. (2002) also examined whether soybean LE influenced oxidative DNA damage in VLBW infants who received parenteral nutrition. In both the LE group (receiving 5.8 ± 1.4 days, $n = 12$) and control group (no LE, $n = 11$), there were no significant differences in urinary 8-hydroxy-2′-deoxyguanosine excretion levels when comparing the LE and control groups before (day 2), during (day 7), and after (day 14) the parenteral LE (Fig. 3). They concluded that parenteral LE did not affect oxidative DNA damage in VLBW infants.

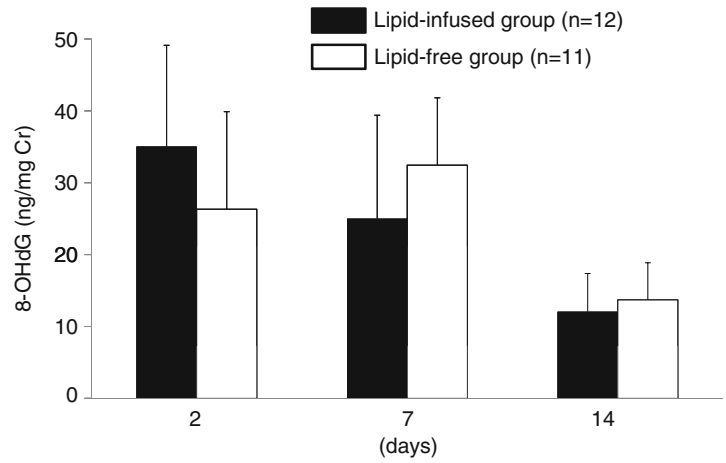

Fig. 3 Changes in urinary 8-hydroxy-2′-deoxyguanosine excretion during the early postnatal period. Values are means + SD standard deviation. *p <0.01 compared with values at 2 and 7 days

CLD has a major impact on long-term outcomes and the quality of life of VLBW infants. Factors predisposing to CLD include low gestational age, respiratory distress syndrome, OS, mechanical ventilation, infection, and undernutrition (Skouroliakou et al. 2012; Gien and Kinsella 2011). Early studies reported that sick premature infants receiving soybean-based LE had an increased incidence of CLD that was attributed to pulmonary fat accumulation resulting in obstruction of the pulmonary capacities (Levene et al. 1984; Hammerman and Aramburo 1988; Puntis and Rushton 1991), whereas other studies showed no increase in the risk of CLD (Alwaidh et al. 1996; Brownlee et al. 1993). A recent study showed that the incidence of CLD was significantly higher in infants receiving soybean-based LE when compared with infants receiving medium-chain triglyceride (MCT)/n-3 PUFA-containing LE (SMOF lipid, Table 1) in VLBW infants (Skouroliakou et al. 2012).

Simmer and Rao (2005) reviewed studies investigating the safety and efficacy of the early introduction of LEs (within the first 5 days after birth) to parenterally fed premature infants. There were no significant differences between the infants of "early" and "not early (from day 6 to 14 after birth)" introduction for the primary end points (e.g., growth, death, and chronic lung disease) of the secondary end points (e.g., incidence of respiratory morbidity, NEC, ROP, sepsis, IVH, and jaundice). They concluded that the early introduction of lipids in PN cannot be recommended for short-term growth or to prevent morbidity and mortality in preterm infants. Nevertheless, because of the theoretical benefit of early administration of lipid emulsions, early introduction may be preferable.

A recent meta-analysis based on five studies including 456 preterm infants also showed that parenteral LEs within the first 2 days of life seem safe and well tolerated (Vlaardingerbroek et al. 2012). Furthermore, the type of LEs did not make a difference in growth of preterm infants during hospital stays. They recommended that the use of lipids within the first few days of life in VLBW infants should not be withheld despite the lack of growth benefits. However, this review shows that LEs that are not purely soybean based (e.g., MCT-soybean, olive-soybean, and soybean-MCT-olive-fish emulsions; Table 1) are weakly associated with fewer episodes of sepsis when compared with pure soybean LEs. This finding might be explained by the lower amount of n-6 fatty acids, because an excess intake of n-6 PUFAs may result in increased synthesis of proinflammatory eicosanoids. In addition, the n-3 fatty acids in fish oil may reduce inflammatory responses while protecting immunity (Grimm et al. 2006).

Large randomized controlled trials (RCTs) are needed to confirm the effect of early LE or the type of LEs on short- and long-term outcomes, including growth, respiratory morbidity, and neurodevelopment, in VLBW infants.

Applications to Other Conditions

Premature neonates with VLBW who receive PN for longer periods are at increased risk of cholestasis and PN-associated liver disease (Fulford et al. 2004). Shin et al. (2008) demonstrated that the cumulative amount of lipid infusion was the only significant independent risk factor of PN-associated cholestasis in preterm infants. The deleterious effects of LEs on the hepatobiliary system have recently been described (Colomb et al. 2000). The accumulation of exogenous lipids in the liver Kupffer cells impairs the clearance of endotoxins, and the peroxidation of lipids produces toxic metabolites (Colomb et al. 2000). Phytosterols contained in lipid emulsions may also have a deleterious effect on biliary secretions (Bindl et al. 2000). A newer lipid emulsion (Omegaven, Table 1) is made from fish oil, which contains LCPUFA (e.g., DHA and EPA). In one study of infants with short bowel syndrome, the reversal of cholestasis due to prolonged PN exposure was quicker in 18 infants who received Omegaven when compared with 21 historical controls who received soybean emulsions (9.4 versus 44 weeks) (Gura et al. 2008). In addition, there were fewer deaths (two versus seven) and liver transplantations (zero versus two) in the Omegaven group than in the soybean LE group. Skouroliakou et al. (2012) compared the effect of two LEs, MCT/n-3 PUFA-containing LE and soybean-based LE on the incidence of PN-associated cholestasis in preterm infants. They concluded that MCT/n-3 PUFA-containing LE did not prevent PN-associated cholestasis, despite a trend toward a lower incidence of cholestasis in preterm infants.

However, RCTs are needed to determine whether this formulation is more beneficial than the soybean-based LE formulations in infants with PN-associated cholestasis.

Guidelines and Protocols

In 2005, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition stated that in newborn infants who cannot receive sufficient enteral feeding, administration of intravenous LEs should be started no later than the third day of life, but may be started on the first day of life (Koletzko et al. 2005). To meet EFA requirements in preterm infants, a minimum dose equal to 0.25 g/kg/day is required, while the amount that can be safely provided as a daily caloric source ranges between 3 and 4 g/kg/day (Koletzko et al. 2005).

Soybean LE is available in Japan in two different concentrations, 10 % and 20 % solutions. At the same dose of lipid, tolerance to and utilization of the infused lipids are better in infants who receive 20 % LE when compared with those who receive 10 % LE, as demonstrated by lower serum concentrations of triglycerides, cholesterol, and phospholipids (Haumont et al. 1989, 1992). The 20 % soybean LE of 0.5 g/kg/day is typically used from 3 days after birth in Japan (Shoji et al. 2011), and increase in increments of 0.5 g/kg/day up to 2 g/kg/day until the intake of enteral feeding was over 50 % of the total water intake. Enteral feeding was typically initiated within the first 8 h after birth (20 mL/kg divided over eight feedings per day).

Tight monitoring of serum triglyceride levels has been recommended in VLBW infants to avoid hypertriglyceridemia as recommended by actual PN guidelines (Koletzko et al. 2005). Recommendations from the European Society for Clinical Nutrition and Metabolism /ESPGHAN state that a concentration of serum triglycerides exceeding 2.82 mmol/L (250 mg/dL) is a critical indication for a reduction in parenteral lipid dose (Koletzko et al. 2005).

Summary Points

- The use of soybean LE in VLBW infants has been limited by concerns regarding impaired lipid tolerance, including impaired pulmonary gas exchange, oxidative stress, and sepsis. This is because the large amounts of LA in soybean LE may further impair LCPUFA formation via substrate inhibition.
- According to a recent meta-analysis and various studies, VLBW infants can tolerate 2 g/kg/day of soybean LE during the first few days of life.

- Newer n-3 PUFAs that contain LE have shown benefit in the treatment of PN-associated cholestasis.
- Further studies are needed to confirm the effect of early LE or the type of LE on short- and long-term outcomes, including growth, respiratory morbidity, and neurodevelopment, in VLBW infants.

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