



The effects of two mixed intravenous lipid emulsions on clinical outcomes in infants after gastrointestinal surgery: a prospective, randomized study

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Abstract

Background There are many advantages of a SMOF emulsion (SMOF-lipid), such as liver-protective properties and anti-inflammatory effects. The objective of this study was to compare the clinical outcomes of SMOF-lipid with medium-chain triglycerides (MCT) /long-chain triglycerides (LCT) in infants after intestinal surgery.

Methods This was a prospective, randomized study. Neonates receiving intravenous nutrient solution, including lipid emulsion after gastrointestinal surgery, were included in this study. The patients were randomly assigned to the SMOF-lipid or MCT/LCT groups. Infants who received intravenous lipid emulsion continuously for > 2 weeks were considered to have completed the study. Differences in weight gain, nutrition indices, alanine transaminase (ALT), aspartate transaminase (AST), and direct bilirubin (DB), and inflammation cytokine markers (interleukin [IL]-6 and tumor necrosis factor [TNF]- α) were measured.

Results The final sample included 160 infants. One hundred fourteen infants received intravenous SMOF-lipid (74) or MCT/LCT (86) > 2 weeks and 46 infants received intravenous SMOF-lipid (22) or MCT/LCT (24) > 4 weeks. There were no significant differences in weight gain, nutrition indices, inflammation cytokine markers, and sepsis between the groups at the end of 2 and 4 weeks; however, in the SMOF group, the ALT, AST, and DB levels were significantly lower than the MCT/LCT group at the end of 4 weeks.

Conclusion The mixture and balanced emulsion of SMOF-lipid was well-tolerated in infants who have undergone gastrointestinal surgery, and liver-protective properties were demonstrated following long-term venous nutrition, especially > 4 weeks.

Keywords Lipid emulsions · SMOF-lipid · Medium-chain triglycerides (MCT)/long-chain triglycerides (LCT) · Infants · Gastrointestinal surgery · Parenteral nutrition

Introduction

Following gastrointestinal surgery, infants often need parenteral nutrition for a long time. Such infants are at a higher risk for nutritional problems, especially in the case of intestinal failure (IF). IF results from gastrointestinal disorders, such as necrotizing enterocolitis, intestinal atresia, gastroschisis, and motility disorders, and is associated

with inadequate promotion of growth and development [1, 2]. Enteral nutrition is preferred for nutritional support in infants after gastrointestinal surgery; however, parenteral nutrition (PN) must be given until enteral nutrition can maintain the nutritional needs, and long-term PN is needed for growth and development of these patients.

Intravenous lipid emulsions (ILEs) are considered to be a standard and important component of PN [3]. ILEs consist of triglycerides, egg phospholipids, and glycerin. ILEs not only provide energy, but also provide fatty acids. There are many kinds of ILEs, including medium-chain triglycerides (MCT)/long-chain triglycerides (LCT), soybean, olive oil, fish oil, structured lipids, and SMOF emulsion (SMOF-lipid). SMOF-lipid is a balanced mixture of MCTs, soybean oil, olive oil, and fish oils at ratios of 30%, 30%, 25%, and

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15%, respectively, with an optimum ω -6: ω -3 ratio and physiologic fatty acid composition [4–6] (Table 1). In an animal model, no cholestasis occurred in the SMOF-lipid group, which suggests no hyperbilirubinemia and no impaired bile flow [7]; thus, the role may be the same as in the study population. In clinical studies, SMOF-lipid was well-metabolized and there are many advantages, such as liver-protective properties and anti-inflammatory effects [8–11].

Given the advantages of SMOF-lipid, we have used SMOF-lipid for infants after intestinal surgery from February 2014. There have been few studies of SMOF-lipid in infants with gastrointestinal surgery and infants with IF. In the current study, we measured postoperative weight gain, nutrition indices, liver function, inflammation cytokine markers, and biochemical indices weekly during the time of PN treatment and compared the clinical outcomes of SMOF-lipid with MCT/LCT in infants after intestinal surgery.

Materials and methods

Subjects

This was a prospective, randomized controlled study. The study was approved by the Ethics Committee of Children's Hospital of Nanjing Medical University. This is a first-class tertiary hospital with an annual operation volume of over 20,000 children, which provides medical treatment for children in Jiangsu province and parts of Anhui Province of China. All the guardians of patients consented to this study. We studied consecutive patients who underwent gastrointestinal surgery in the Department of Neonatal Surgery at Children's Hospital of Nanjing Medical University between February 1, 2014 and January 31, 2018. The exclusion criteria were as follows: continuous intravenous ILE for less than 2 weeks and a pre-existing hepatobiliary disease.

The study groups were assigned according to randomly assigned numbers. All infants who had undergone

gastrointestinal surgery and received lipid emulsion were assigned random numbers and then divided into the SMOF-lipid group or the MCT/LCT group. A total of 500 cases were collected from the beginning of February 1, 2014. This was a single-blind study, and for blinding, only patients and their parents were not known the allocation to the groups.

Then, we divided these patients into four groups according to the lipid emulsion types and the duration of the use of lipid emulsion: The SMOF-2w group (which received intravenous SMOF-lipid > 2 weeks), the MCT/LCT-2w group (which received intravenous MCT/LCT > 2 weeks), the SMOF-4w group (which received intravenous SMOF-lipid > 4 weeks), and the MCT/LCT-4w group (which received intravenous MCT/LCT > 4 weeks).

“All in-One” solution was used for PN, consisting of carbohydrates, lipid emulsion, amino acids, electrolyte, fat-soluble vitamins, and water-soluble vitamins. The intravenous nutrient solution was maintained for 20–24 h through the micropump input. The initial dose of lipid emulsion (SMOF-lipid C_{6–24} [Fresenius Kabi Asutria GmbH, Zweigniederlassung Linz, Austria] or MCT/LCT C_{8–24} [Baxter Qiaoguang, Healthcare Co., Ltd, Guangzhou, China]) was 1 g/kg/d, and the dose was gradually increased to 3 g/kg/d. The initial dose of amino acids was 1 to 2 g/kg/d, and the dose was gradually increased to 3 to 4 g/kg/d. Carbohydrates provided 20–40% of non-protein energy. Fat- and water-soluble vitamins were added to the nutrient solution.

The same enteral nutrition support protocol was used for all groups. Specifically, minimal enteral nutrition feeding (10 mL/kg/d for 2 days, then an increase of 5 mL/kg/d) was initiated when normal defecation exhaust of the stoma or anus and/or bilious gastric residual was absent. If the infant's mother could provide milk, that was the first choice for nutrition.

Differences in weight gain, nutrition indices, alanine transaminase (ALT), aspartate transaminase (AST), direct bilirubin (DB), inflammation cytokine markers [interleukin (IL)-6 and tumor necrosis factor (TNF)- α] were measured.

Statistical analysis

Statistical analysis was carried out using SPSS software (version 20.0; SPSS, Inc., Chicago, IL, USA). Data are expressed as mean \pm standard deviation (SD). Parameters were analyzed by independent sample *t* tests or analysis of variance (ANOVA). A Pearson χ^2 test was used to compare the sepsis ratio between the groups. For the aforementioned parameters, a *P* < 0.05 was considered statistically significant. Time on PN is compared by log-rank test.

Table 1 Composition of lipid emulsions

Ingredient	SMOF-lipid C _{6–24}	MCT/LCT C _{8–24}
Soybean oil (g/100 mL)	6	10
MCTs (g/100 mL)	6	10
Olive oil (g/100 mL)	5	–
Fish oil (g/100 mL)	3	–
Egg-yolk phospholipids (g/100 mL)	1.2	1.2
Glycerol (g/100 mL)	2.5	2.5
α -Tocopherol (mg/L)	20	11
Total energy (kcal/100 mL)	200	190.8

MCTs medium-chain triglycerides

Results

Patients

A total of 500 cases were collected, including 250 cases in the SMOF-lipid group and 250 cases in the MCT/LCT group. The final sample included 160 infants who had undergone gastrointestinal surgery and received lipid emulsion (SMOF-lipid or MCT/LCT) for more than 2 weeks: the SMOF-2w group ($n=74$ patients), the MCT/LCT-2w group ($n=86$ patients), the SMOF-4w group ($n=22$ patients), and the MCT/LCT-4w group ($n=24$ patients) (detailed information about these patients is provided in Fig. 1; Table 2). There was no significant statistical difference in time on PN ($P=0.253$, Fig. 2). Nutritional intakes are shown in Table 3.

Postoperative weight gain

The weight gain in the MCT/LCT-2w group was 2.5 ± 0.5 g/d (week 1) and 3.7 ± 1.4 g/d (week 2). The weight gain in the SMOF-2w group was 2.7 ± 0.5 g/d (week 1) and 3.4 ± 1.2 g/d (week 2). There was no statistically significant difference between the MCT/LCT-2w and SMOF-2w groups at the end of weeks 1 and 2. The weight gain in the MCT/LCT-4w group was 2.5 ± 1.1 g/d (week 1), 3.7 ± 1.0 g/d (week 2), 3.4 ± 1.2 g/d (week 3), and 4.1 ± 0.7 g/d (week 4). The weight gain in the SMOF-4w group was 2.7 ± 1 g/d (week 1), 3.4 ± 1.5 g/d (week 2), 3.3 ± 0.5 g/d (week 3), and 4 ± 1.4 g/d (week 4). There was no statistically significant difference between the MCT/LCT-4w and SMOF-4w groups at the end of weeks 1, 2, 3, and 4.

Laboratory testing for liver function

The ALT, AST, and DB levels were not significantly different between the MCT/LCT-2w and SMOF-lipid-2w groups at baseline and at the end of weeks 1 and 2. The levels of ALT were also not significantly different between the MCT/LCT-4w and SMOF-lipid-4w groups at baseline and at the end of weeks 1 and 2; however, ALT was decreased in the SMOF-lipid-4w group at the end of weeks 3 ($P < 0.05$) and 4 ($P < 0.05$). The AST and DB levels were not significantly different between the MCT/LCT-4w and SMOF-lipid-4w groups at baseline and at the end weeks 1, 2, and 3; however, AST and DB were decreased in the SMOF-lipid-4w group at the end of week 4 ($P < 0.05$) (Fig. 3).

Nutrition indices

The pre-albumin levels were not significantly different between the MCT/LCT-2w and SMOF-lipid-2w groups at baseline and at the end of weeks 1 and 2. The levels retinol-binding protein were not significantly different between the MCT/LCT-2w and SMOF-lipid-2w groups at baseline and at the end of weeks 1 and 2. The pre-albumin levels were not significantly different between the MCT/LCT-4w and SMOF-lipid-4w groups at baseline and at the end of weeks 1, 2, 3, and 4. The retinol-binding protein levels were not significantly different between the MCT/LCT-4w and SMOF-lipid-4w groups at baseline and at the end of weeks 1, 2, 3, and 4 (Fig. 4).

Fig. 1 A total of 500 cases were collected, including 250 cases in the SMOF-lipid group and 250 cases in the MCT/LCT group. The final sample included 160 infants who had undergone gastrointestinal surgery and received lipid emulsion (SMOF-lipid or MCT/LCT) for more than 2 weeks: the SMOF-2w group ($n=74$ patients), the MCT/LCT-2w group ($n=86$ patients), the SMOF-4w group ($n=22$ patients), and the MCT/LCT-4w group ($n=24$ patients)

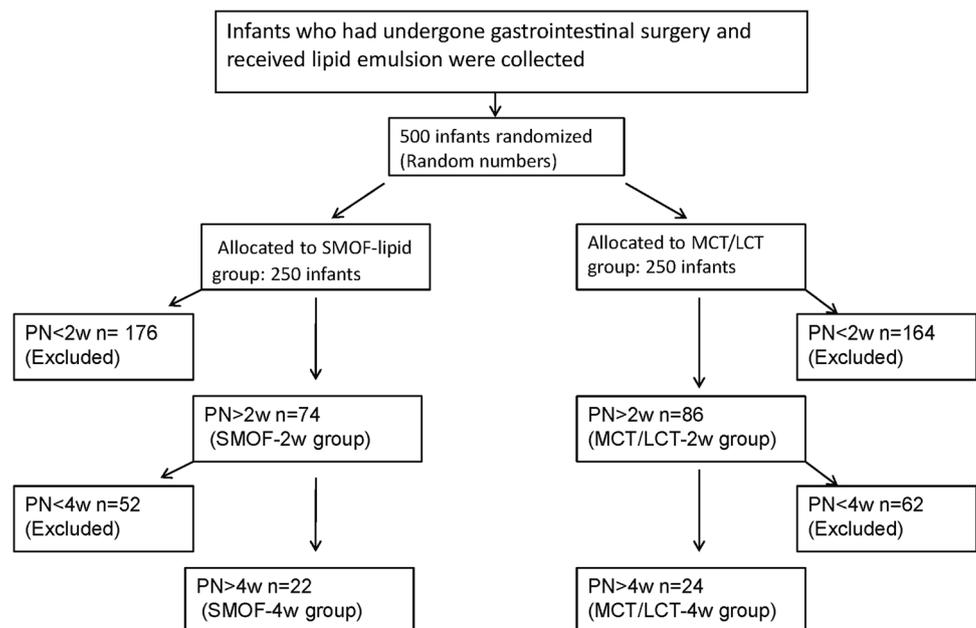
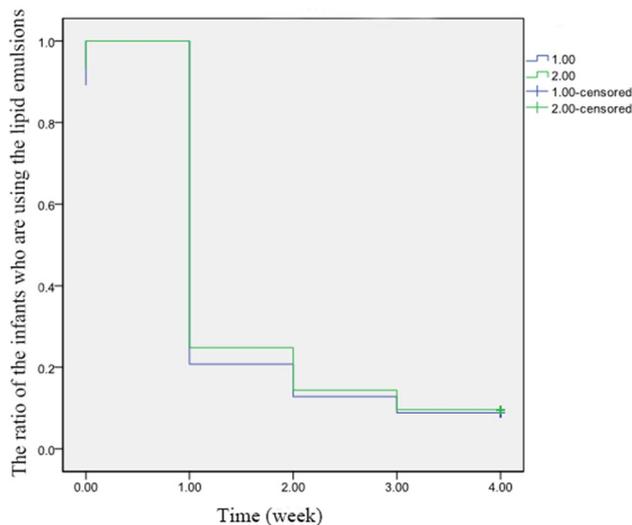


Table 2 Baseline demographic data and main diagnoses of SMOF-lipid-2w, MCT/LCT-2w SMOF-lipid-4w, and MCT/LCT-4w patients

	SMOF-lipid-2w	MCT/LCT-2w	<i>P</i>
Age (days), mean (SD)	4.8 (3.6)	4.7 (3.5)	0.966 ^a
Gender (male/female)	74 (29/35)	86 (45/41)	0.395 ^b
The types of diseases included in each group			0.937 ^b
Necrotizing enterocolitis	33	37	
Intestinal atresia	28	30	
Annular pancreas	7	8	
Intestinal neuron dysplasia	3	4	
Gastric perforation	2	4	
Gastroschisis	1	3	
	SMOF-lipid-4w	MCT/LCT-4w	<i>P</i>
Age (days), mean (SD)	5 (2.8)	4 (1.9)	0.069 ^a
Gender (male/female)	22(10/12)	24(13/11)	0.555 ^b
The types of diseases included in each group			0.874 ^b
Necrotizing enterocolitis	10	11	
Intestinal atresia	9	8	
Intestinal neuron dysplasia	2	3	
Gastric perforation	0	1	
Gastroschisis	1	1	

^aStudent's *t* test^bTwo-sided χ^2 test**Fig. 2** The ratio of the infants who are using the lipid emulsions

Indicators of inflammatory status

The levels of the inflammatory cytokine markers, IL-6 and TNF- α , were not significantly different between the MCT/LCT-2w and SMOF-lipid-2w groups at baseline, and at the end of weeks 1 and 2. The IL-6 and TNF- α levels were not significantly different between the MCT/LCT-4w and

Table 3 Nutrient intakes

Nutrient intakes	SMOF-lipid	MCT/LCT	<i>P</i> value
Energy intake at day 14			
Total (EN + PN) (kcal/kg d)	105.5 \pm 12.7	104 \pm 6.2	0.346
EN intake (kcal/kg d)	52.9 \pm 16.6	48.2 \pm 17.6	0.46
PN intake (kcal/kg d)	52.6 \pm 15.6	55.8 \pm 16.1	0.764
Energy intake at day 28			
Total (EN + PN) (kcal/kg d)	108.7 \pm 6.9	103.8 \pm 6	0.908
EN intake (kcal/kg d)	68.3 \pm 17.6	63 \pm 16.2	0.874
PN intake (kcal/kg d)	40.4 \pm 14.4	40.9 \pm 16.9	0.876

EN enteral nutrition, PN parenteral nutrition

SMOF-lipid-4w groups at baseline, and at the end of weeks 1, 2, 3, and 4 (Fig. 5).

Sepsis incidence

The incidence of sepsis was not significantly different between the MCT/LCT-2w, SMOF-lipid-2w, MCT/LCT-4w, and SMOF-lipid-4w groups (Fig. 6).

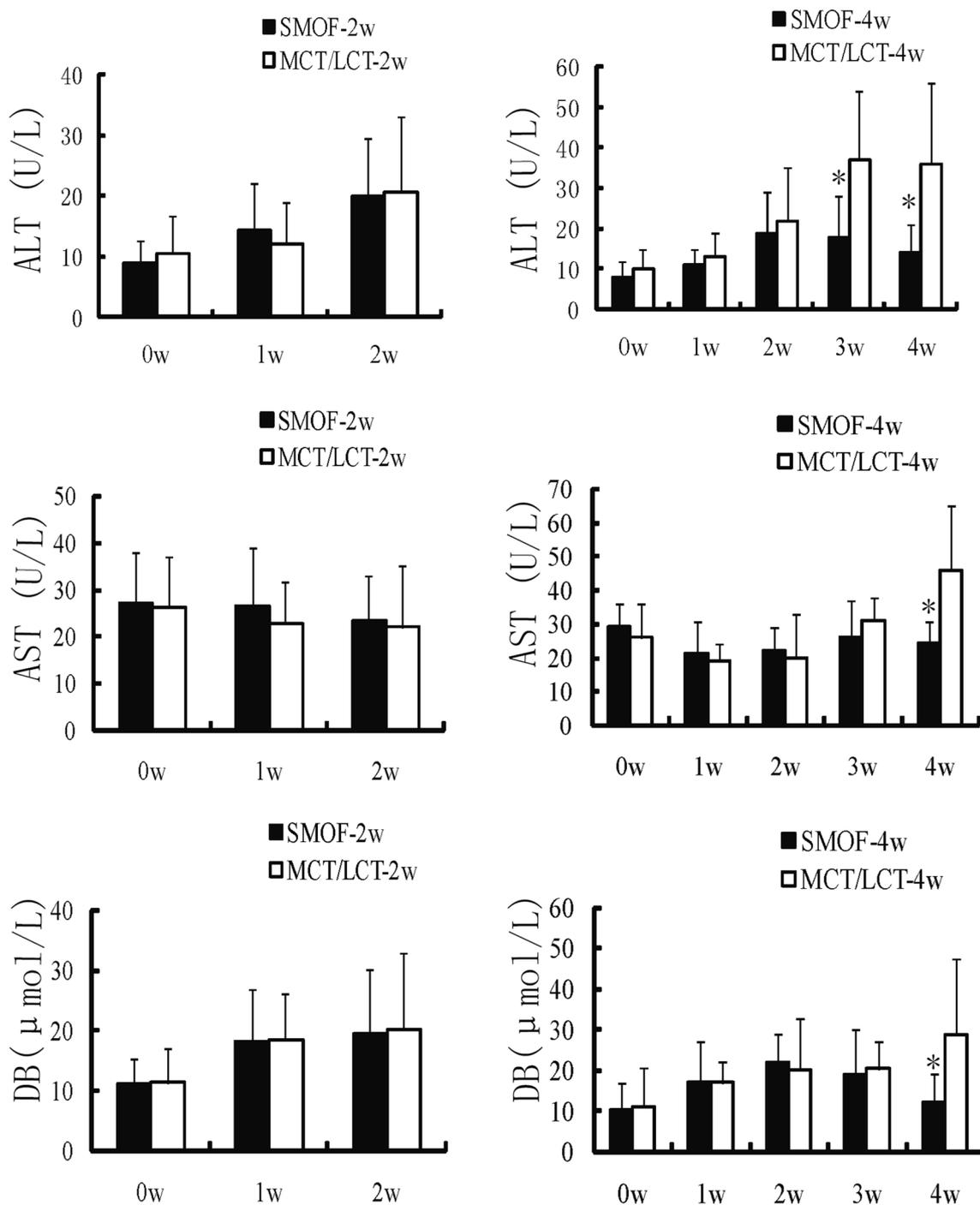


Fig. 3 The ALT, AST, and DB levels in the infants in the study. **a** ALT of the SMOF-lipid-2w group. **b** ALT of the SMOF-lipid-4w group. **c** AST of the SMOF-lipid-2w group. **d** AST of the SMOF-lipid-4w group. **e** DB of the SMOF-lipid-2w group. **f** DB of the

SMOF-lipid-4w group. The ALT (**b**) levels decreased with SMOF-lipid at the end of weeks 3 and 4. The AST (**d**) and DB (**f**) levels decreased with SMOF-lipid at the end of week 4. * $P < 0.05$

Discussion

This work represents a randomized clinical study involving infants who received PN for more than 2 weeks after gastrointestinal surgery. The two mixed-lipid emulsions

(SMOF-lipid and MCT/LCT) were shown to be safe over a period of 4 weeks. However, in the SMOF-lipid group, ALT, AST, and DB were significantly lower than those in the MCT/LCT group at the end of 4 weeks.

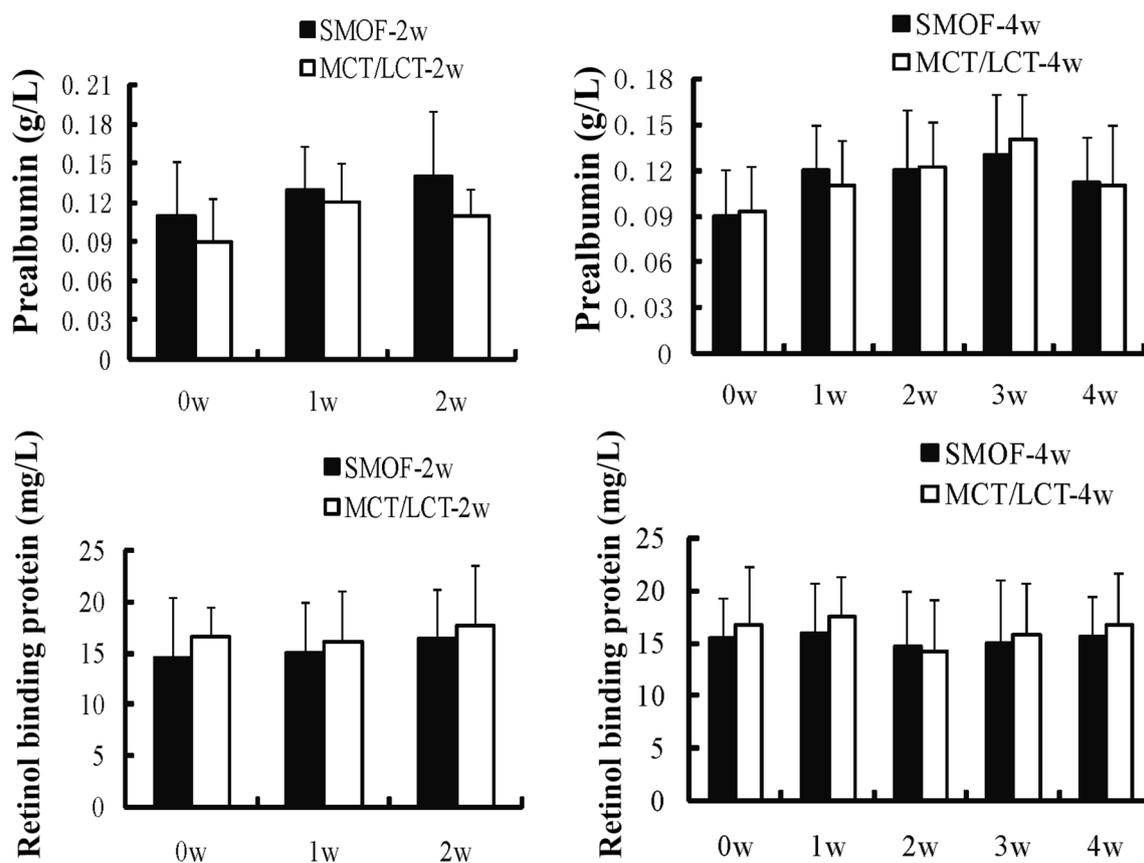


Fig. 4 The pre-albumin and retinol-binding protein levels in the infants in the study. **a** Pre-albumin of the SMOF-lipid-2w group. **b** Pre-albumin of the SMOF-lipid-4w group. **c** Retinol-binding protein of the SMOF-lipid-2w group. **d** Retinol-binding protein levels in the SMOF-lipid-4w group. The pre-albumin and retinol-binding protein

were not significantly different between the MCT/LCT-2w group and the SMOF-lipid-2w group at baseline and at the end of weeks 1 and 2. The pre-albumin and retinol-binding protein levels were not significantly different between the MCT/LCT-4w and SMOF-lipid-4w groups at baseline and at the end of weeks 1, 2, 3, and 4

Nutritional support is important in the recovery, growth, and development of infants after intestinal surgery. Lipid emulsions are a constituent of PN and provide an important source of essential fatty acids and non-carbohydrate energy in venous nutritional supplements [12, 13]; however, there are many complications associated with PN. For example, intravenous use of lipid emulsions for a long period of time may increase the possibility of injury to the liver, leading to cholestasis and hepatic steatosis. In addition, the intravenous use of lipid emulsions for a long period of time may lead to metabolic and immune disorders [5, 14–17].

The ideal multiple strategies to avoid parenteral nutrition-associated liver disease (PNALD) in post-surgical infants are to gradually reintroduce enteral nutrition [18] using a low dosage of intravenous fat emulsions [19], using parenteral fish oil or fish oil-based lipid emulsions (Omegaven and SMOF) [20–23], and preventing catheter-related sepsis and reducing bloodstream infections by using ethanol lock therapy and oral antibiotics [24]. The criteria for IF-associated liver disease include infant use of PN for longer

than 2 weeks and a serum DB concentration greater than 2 mg/dL. Thus, we included patients who used intravenous nutrition for longer than 2 weeks in this study to compare the results of using different lipid emulsions for approximately 2 weeks. Moreover, there are studies on the merits of SMOF-lipid on liver function; the liver enzyme and total bilirubin levels of the patients were significantly lower after 4 weeks of treatment [9], and complications of long-term PN were more likely to occur in the IF patients (defined as use of intravenous nutrition > 28 days) [25]. We included IF patients who used intravenous nutrition for longer than 4 weeks to study the other two groups. Basal liver enzyme and serum DB levels were not different between the four groups, and liver enzyme and serum DB levels were not different between the two groups at the end of the first and second weeks; however, liver enzyme and serum DB levels in the SMOF-lipid group were lower at the end of the fourth week. This result is consistent with the study of Goulet [26], who showed that compared with controls receiving a soybean oil emulsion, total bilirubin was decreased in children

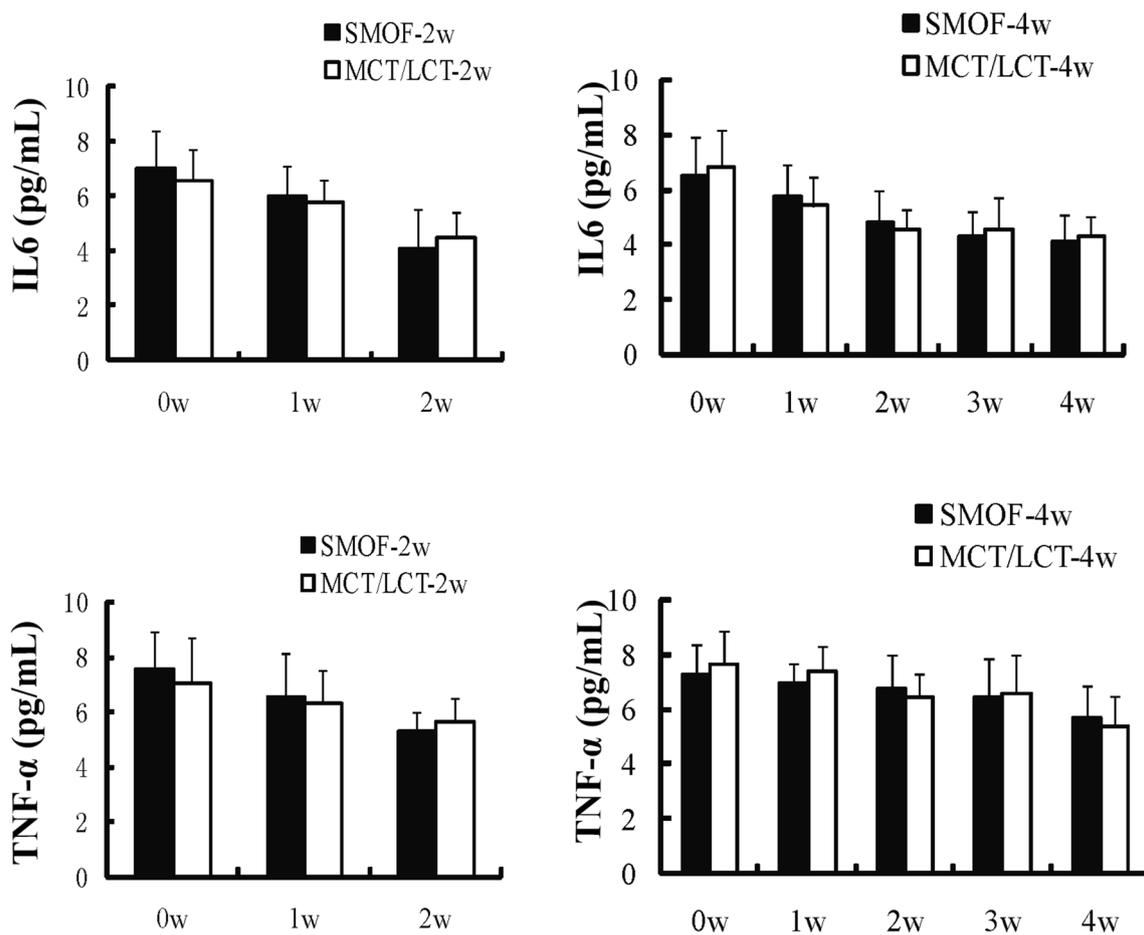


Fig. 5 The IL-6 and TNF- α levels in the infants in the study. **a** IL-6 of the SMOF-lipid-2w group. **b** IL-6 of the SMOF-lipid-4w group. **c** TNF- α of the SMOF-lipid-2w group. **d** TNF- α of the SMOF-lipid-4w group. The IL-6 and TNF- α levels were not significantly different

between the MCT/LCT-2w and SMOF-lipid-2w groups at baseline and at the end of weeks 1 and 2. The IL-6 and TNF- α levels were also not significantly different between the MCT/LCT-4w and SMOF-lipid-4w groups at baseline and at the end of weeks 1, 2, 3, and 4

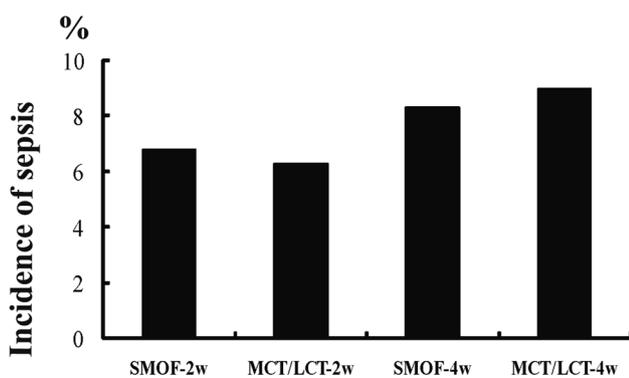


Fig. 6 The incidence of sepsis in the infants in the study. The incidence of sepsis was not significantly different between the MCT/LCT-2w, SMOF-lipid-2w, MCT/LCT-4w, and SMOF-lipid-4w groups

on home PN with SMOF-lipid after 4 weeks. The long-term use of SMOF-lipid demonstrated the protective effect of SMOF-lipid on the liver. The liver-protective properties of SMOF-lipid are consistent with a previous study [9], which may be due to the fact that SMOF-lipid contains fish oil, and the omega-3 polyunsaturated fatty acids (PUFAs) from fish oil have a therapeutic effect on PN-associated cholestasis [27, 28]; in addition, fish oil has a lower concentration of phytosterols [29].

It remains controversial whether SMOF-lipid is superior to other lipid emulsions in terms of complications. Angsten et al. [30] showed a significantly higher number of septic episodes in the SMOF-lipid group than in the standard lipid emulsion group, but Deshpande et al. [31] showed the incidence of sepsis between the SMOF-lipid and olive oil lipid groups was not significantly different. In our study, we found that the incidence of sepsis between the SMOF-lipid and MCT/LCT groups was not significantly different in the 2- and 4-week groups in infants after gastrointestinal

surgery. The incidence of sepsis has multiple factors and may also be associated with the original infectious disease of the infants, the level of catheter care, hand hygiene, local flora, and availability of prenatal care. With improvement in the level of catheter care, sepsis has now been reduced to a very low level.

A previous study showed that postoperative patients had lower TNF- α and IL-6 levels with SMOF-lipid than patients receiving an olive/soybean oil lipid emulsion [32]. In our study, there was no significant difference in inflammatory cytokine markers between the groups. The anti-inflammatory effect of SMOF-lipid is still important for children with short bowel syndrome because children with short bowel syndrome often have infections caused by intestinal flora disorder. SMOF-lipid is a mixture of soybean oil, olive oil, and fish oils, and olive oil has indirect anti-inflammatory activity by replacing ω -6 fatty acids with oleic acid, and fish oil can inhibit the inflammatory reaction, such as alleviate cytokine release and adhesion molecule expression, balancing the immune system by the long-chain ω -3 fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] [33, 34]. Moreover, ω -3 PUFA has the effect of regulating immunity and alleviating inflammation, primarily because ω -3 PUFA can be incorporated into the cell membranes and act as a lipid mediator precursor [35]. After antigenic stimulation, ω -3 PUFA and ω -6 PUFA participate in the inflammatory response by competitive signal pathways that are used to synthesize eicosanoids [36]. Eicosanoids generated by ω -3 PUFA are less inflammatory [14], and the optimal ω -6: ω -3 ratio reduces the levels of pro-inflammatory mediators, which is potentially beneficial for alleviating the inflammatory response and immunosuppression in critically ill patients. SMOF-lipid has a lower ω -6: ω -3 fatty acid ratio (approx. 2.5:1), thus resulting in fewer complications [32, 37].

When enteral nutrition cannot meet the nutritional demand for infants, adequate PN is important to support brain growth and cognitive development. Especially for premature infants, optimizing nutritional support is key for improving neurodevelopment [38]. Moreover, EPA and DHA, which are in lipid emulsions, are crucial for growth and development of the brain and retina [39, 40]. In a previous study, the Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III) was used in assessing the neurodevelopment by a trained psychologist at 6 and 24 months corrected age, and parents completed the Parent Report of Children's Abilities (PARCA-R) at 24 months corrected age. The results show that there were no differences between the two intravenous lipid emulsion (Intralipid and Omegaven) groups in language, cognitive, or motor outcomes [41]. Since our research duration was 4 weeks, there is no comparison of brain development in our study. In the subsequent study, we will compare the effects of lipid emulsions on

brain development. Magnetic resonance imaging (MRI) is another helpful tool to estimate preterm brain development [42]. However, it is difficult for children to undergo MRI under natural sleep, and they require sedation treatment; thus, only a few patients are evaluated, giving us insufficient results.

Some current reports have suggested that liver biopsy is a better indicator of persistent or progressive fibrosis of intestinal failure associated liver disease (IFALD) compared with DB, because potentially progressive fibrosis is persistent in the setting of normal direct bilirubin and inflammatory markers [43]. However, some patients did not have complete resolution of liver biochemistry [43]. In our study, because of the risk involved with liver biopsy, we still use direct bilirubin for research, which is a limitation. Other limitations of this study include that it is a single center, small sample size study, it did not have a long follow-up period, and it was not a double-blind study.

In conclusion, in infants who have undergone gastrointestinal surgery, the new balanced emulsion SMOF-lipids are well-tolerated and have a favorable effect on long-term venous nutrition, especially over 4 weeks.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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