European Journal of Clinical Nutrition (2014), 1–7

www.nature.com/ejcn

ORIGINAL ARTICLE

Comparison of liver function with two new/mixed intravenous lipid emulsions in children with intestinal failure

J Pichler[1,2], V Simchowitz[3], S Macdonald[4] and S Hill[1]

BACKGROUND/OBJECTIVE: The high incidence of liver disease associated with intravenous soybean lipid has led to development and use of alternative intravenous lipid emulsions (ILEs). The aim of this study was to compare two new/mixed ILEs: a medium-chain triglyceride (MCT) combined with soybean (i.e., Lipofundin) and a combination of both these lipids with additional olive and fish oils (SMOF).

SUBJECTS/METHODS: Neonates/premature infants newly starting parenteral nutrition (PN) treatment and children with abnormal liver function tests, alanine transferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transferase (γ-GT) 1.5x upper limit of normal and/or total bilirubin >50 μmol/l for >2 weeks on treatment with PN containing pure soybean ILE (Intralipid 20%; Fresenius Kabi), were started on/changed to either SMOF or Lipofundin. Results of biochemistry and clinical outcome were compared on commencing and discontinuing treatment according to the new ILE used.

RESULTS: One hundred and twenty-seven children aged 0–16 (median 0.6) years were included. Fifty-six were given Lipofundin and 71 SMOF. Fifty-three of 127 started PN for the first time and 74 had had previous treatment with Intralipid. During treatment, ALT and ALP levels fell significantly ($P < 0.008$ on SMOF; $P < 0.05$ on Lipofundin), with additional significant reduction in γ-GT with SMOF. Hyperbilirubinaemia incidence decreased from 34% on starting to 24% on discontinuing treatment ($P \leqslant 0.05$). Infection rate/1000 catheter days, full blood count, serum triglyceride and cholesterol levels were similar with both ILEs.

CONCLUSION: Addition of MCT to soybean ILE was associated with improved liver function. There was an even greater improvement when olive and fish oils were also added with higher incidence of resolution of abnormal liver function tests and reduced inflammation.

European Journal of Clinical Nutrition advance online publication, 25 June 2014; doi:10.1038/ejcn.2014.118

INTRODUCTION

Parenteral nutrition (PN) is effective supportive treatment for severe intestinal failure (IF).1 A common and potentially life-threatening complication is IF-associated liver disease (IFALD). Major risk factors for IFALD include prematurity, lack of enteral intake, recurrent catheter-related bloodstream infection (CRBSI)/sepsis and duration and components of PN.[1–5] Constituents of PN solutions implicated in the aetiology of IFALD include excess carbohydrates, amino acids and, perhaps most commonly, lipid.[1,6] Intravenous lipid emulsions (ILEs) are incorporated in PN to provide an energy-dense source of non-protein calories and essential fatty acids (EFAs).[2]

The precise manner in which ILEs contribute to IFALD is unclear and probably involves multiple mechanisms.[1,4,5,7–9] The first safe ILE developed was derived from soybean oil.[10] Soybean provides Ω-6 long-chain polyunsaturated fatty acids[11] and minimal amounts of Ω-3. Problems associated with the use of Ω-6 fatty acids include reduced biliary secretion,[12,13] promotion of an inflammatory response and impaired immunity.[14,15] The phytosterol component of soybean has been associated with liver disease.[12,13]

In contrast, reversal of severe cholestasis in infants has been described with a pure Ω-3 fish oil-based ILE (Omegaven 10%; Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany).[4,7,16–24] In addition, mixed ILEs containing olive oil and medium-chain triglyceride (MCT) have also been associated with less IFALD.[25–29]

Although safety data using mixed ILEs have been published for premature infants[28] and children on long-term/home PN,[27] previous studies have not compared efficacy of different ILEs. The aim of this study was to compare safety and efficacy of two new ILEs: Lipofundin, composed of MCT and long-chain triglycerides 20% (a physical mixture, 1:1 by weight, of soybean and coconut oil; Lipofundin, B-Braun) and SMOFlipid 20% (a physical mixture of 30% soybean, 30% MCT, 25% olive and 15% fish oil; SMOF, Fresenius Kabi) in terms of safety, weight gain and outcome in hospitalised children receiving PN.

MATERIALS AND METHODS

Study population

The study was performed retrospectively in a specialist paediatric hospital from November 2006 to September 2010. Please see Table 1 for details of the ILEs used. Standard ILE was pure soybean (Intralipid 20%; Fresenius Kabi). Patients were treated with new ILEs in the following circumstances:

(1) Patients already on Intralipid (ranging from 0.5 to 3 g/kg per day) were changed to a new ILE if IFALD (defined as alkaline phosphatase (ALP),

[1]Department of Paediatric Gastroenterology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [2]Department of Paediatric and Adolescent Medicine, Medical University of Vienna, Vienna, Austria; [3]Department of Pharmacy, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK and [4]Department of Dietetics, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK. Correspondence: Dr J Pichler, Department of Paediatric Gastroenterology, Great Ormond Street Hospital for Children NHS Foundation Trust, London WC1N 3JH, UK.
E-mail: Judith.pichler@meduniwien.ac.at
Received 15 December 2013; revised 9 May 2014; accepted 15 May 2014

Table 1. Comparison and characteristics of parenteral lipid emulsions

Product *Manufacturer* *(20 g/100 ml)*	*Intralipid 20%* *Baxter Healthcare/Fresenius Kabi*[a]	*SMOF 20%* *Fresenius Kabi*[b]	*Lipofundin MCT 20%* *B-Braun*[c]
Oil source (g)			
Soybean	20	6	10
MCT	0	6	10
Olive oil	0	5	0
Fish oil	0	3	0
α-Tocopherol (mg/l)	~38	~200	~200
Phytosterol (mg/l)	348 ± 33	47.6	~125 NR
Fat composition (g)			
Linoleic	5	2.9	2.7
α-Linolenic	0.9	0.3	0.4
EPA	0	0.3	0
DHA	0	0.05	0
Oleic	2.6	2.8	1.1
Palmitic	1	0.9	0.7
Stearic	0.35	0.3	0.2
Arachidonic	0	0.05	0.02

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MCT, medium-chain triglyceride; NR, not reported. Data were provided by each manufacturer. [a]Intralipid; Baxter Healthcare/Fresenius Kabi (Deerfield, IL, USA). [b]SMOFlipid (Fresenius Kabi Austria GmbH, Graz, Austria). [c]Lipofundin (50% soybean oil, 50% coconut oil; B. Brau Melsungen AG, Melsungen, Germany).

alanine aminotransferase (ALT) or γ-glutamyl transferase (γ-GT)) increased to 1.5 times the upper limit of the reference range or total bilirubin >50 μmol/l (⩾2.9 mg/dl) for ⩾2 weeks developed.

(2) Premature infants <36 weeks gestation expected to need prolonged PN for >2–3 weeks and therefore at high risk of IFALD, for example, postgastrointestinal surgery, [30,31] were treated with Lipofundin or SMOF on commencing PN.

The same criteria were used to change or start either new mixed ILE. Lipofundin was available from the start of the study period and SMOF from when licensed in 2009. Other than changing from 70% isopropanol to 2% chlorhexidine in 70% isopropanol to disinfect connectors and catheter hubs for connecting/disconnecting PN infusions, there were no changes in practice during the period studied.

Study design

Details of patients treated with new ILEs were obtained from hospital pharmacy records. Additional clinical information taken from patients' medical records included gender, age, primary diagnosis, prematurity and gestational age, length of hospitalisation and treatment with ursodexoycholic acid (15–30 mg/kg per day). Outcome of IF was recorded including development of enteral autonomy,that is, successful weaning from PN to enteral feed, persistent IF (children discharged home on PN), small bowel/liver transplantation or death. Cause of death if potentially related to PN, for example, sepsis or liver failure was recorded.

Outcome of three higher risk groups, that is, total hyperbilirubinaemia >50 μmol/l (⩾2.9 mg/dl) for ⩾2 weeks, neonates/infants aged <1 year and patients treated with PN >27 days,[32] were reviewed separately.

Parenteral nutrition

PN-related factors documented were days on treatment, weight gain, volume and calories prescribed, carbohydrate, amino acid and nitrogen intake, ILE type and average dose of total lipid and dose of soybean ILE component (g/kg per infusion) administered. Energy and protein provision was concordant with 2005 ESPGHAN/ESPEN guidelines.[33] PN was 'cycled' as soon as blood glucose was maintained off PN. Enteral feed was introduced when 0.5 ml/h was tolerated.

Laboratory safety parameters and outcome

Laboratory data recorded on starting and stopping PN included albumin to indicate liver synthesis, ALT as a liver enzyme marker, and total and conjugated bilirubin, γ-GT and ALP to assess cholestasis. Metabolic measurements included serum triglycerides, cholesterol and coagulation markers: platelets, prothrombin time (PT) and fibrinogen. Additional safety indices included full blood count and C-reactive protein (CRP).

CRBSI episodes/1000 central venous catheter (CVC) days were recorded. CRBSI was diagnosed when blood culture was positive with no other infective focus. Broad-spectrum antibiotics were administered via the CVC, and then tailored according to sensitivities of cultured bacteria.

Ethics

The study was approved by the Chair of the Local Research Ethics Committee. Further formal ethical consideration was considered unnecessary.

Statistics

Statistical analyses were performed with SPSS Software (version 18.0 Mac; SPSS, Chicago, IL, USA). Continuous variables were presented as median, minimum and maximum values, and categorical data as absolute frequencies and proportions. Fisher's exact test was used for comparisons of proportions and paired *t*-test and *t*-test for continuous data. *P*-value of <0.05 was considered significant.

RESULTS

Patient demographics

One hundred and twenty-seven children (67 (53%) male, 60 (47%) female) were treated; 71 with SMOF and 56 with Lipofundin (Table 2). Fifty-three patients were started on a new ILE at the time of commencing PN and 74 were transferred from Intralipid. Age on starting treatment ranged from birth to 16 years, with a median of 0.4 years for SMOF and 0.7 years for Lipofundin ($P=0.05$ for age difference).

Seventy-four (58%) patients had previously had Intralipid for 19–154 days, with a median of 73 at 2.5–3 g/kg per infusion. New ILEs were given for 20–89 days, with a median of 29 days. Mean total ILE administered/infusion was 2.3 g ± 0.8 SMOF and 2.2 g ± 0.9 Lipofundin, with a range of 0.5–3 g/kg per infusion. The mean soybean content of the ILEs was 0.8 g ± 0.3 in SMOF and 1.1 g ± 0.4 in Lipofundin ($P<0.001$). Macronutrients infused were similar in both groups ($P=$ not significant).

No adverse effects were detected and significant weight gain was achieved with both new ILEs (see Table 3 for details). Children had significantly lower albumin on starting SMOF (mean 27 g/l ± 5 compared with 29 g/l ± 6 with Lipofundin, $P=0.03$). Albumin increased significantly with both ILEs, but remained significantly lower with SMOF.

CRP levels decreased with both lipids: 46 mg/l ± 49 to 22 mg/l ± 38 ($P=0.02$) with SMOF and 35 mg/l ± 31 to 26 mg/l ± 32 with Lipofundin. The reduction was significantly greater with SMOF ($P=0.2$).

Incidence of CRBSI/1000 CVC days, full blood count, serum triglyceride and cholesterol levels were similar with both ILEs. There was no hypertriglyceridemia. Eighty-four (66%) patients weaned off PN by the end of the study period, 20 (16%) patients died (17.85% death non-PN-related and 3.15% associated with sepsis and liver failure) and 23 (18%) were discharged home on PN. None of the children were eligible for or underwent small intestinal or liver transplant.

Liver enzymes and bilirubin levels were similar in both new ILE groups on starting treatment (see Table 3 and Figure 1 for details). There was significant reduction in ALT and ALP with both ILEs with additional significant reduction in γ-GT with SMOF. On completing treatment, ALT was significantly lower with SMOF than with Lipofundin ($P=0.01$). There were no significantly different changes in total/conjugated bilirubin levels when the two ILEs were compared. Ninety-one patients were treated ursodeoxycholic acid, including 26/59 (44%) SMOF and 14/32 (44%) Lipofundin.

Table 2. Baseline demographic characteristics of patients according to the type of lipid

	SMOF	*Lipofundin*	*Total*	P-*value*
Number (male %)[a]	71 (62%)	56 (41%)	127 (53%)	
Premature	19 (27%)	15 (26%)	34 (27%)	0.5
Gestational week[b]	30 (22–35)	26 (24–33)	29 (22–35)	0.06
Ursodeoxycholic acid	26/59 (44%)	14/ 32 (44%)	40/91 (44%)	
Diagnoses				
Primary digestive disorders	45 (63%)	36 (64%)	81 (64%)	0.5
Surgical	31	28	59	
Short bowel syndrome	16	15	31	
Necrotising enterocolitis	15	13	28	
Gastrointestinal	14	8	22	
Motility disorders	4	3	7	
Enteropathy	5	3	8	
Crohn's disease	2	—	2	
Others	3	2	5	
Surgical procedures	29 (41%)	24 (43%)	53 (42%)	0.4
Primary non-digestive disorder	26 (37%)	20 (36%)	46 (36%)	0.5
Haematology/Oncology	13	12	25	
Transplant (bone marrow, heart, lung, kidney)[a]	15 (21%)	9 (16%)	24 (19%)	0.5
Cardio/thoracic	7	8	15	
Others	6	—	6	
Parenteral nutrition				
Age of start PN (years)[b]	0.4 (birth–15.8)	0.7 (birth–16)	0.6 (birth–16)	0.05
Duration of PN (days)	41 (3–311)	30 (3–436)	34 (3–436)	0.2
Number of children with PN before starting Lipofundin/SMOF	35 (49%)	39 (70%)	74 (58%)	0.03
Days of PN before starting Lipofundin/SMOF	40 (6–435)	41 (6–213)	40 (6–435)	0.8
Soybean amount (g/kg per infusion)	2.3 ± 0.8, 0.5–3	2.2 ± 0.9, 0.5–3		0.2
Parenteral nutrition intake (kg per day[c])				
Volume (ml/kg)	90 ± 35	104 ± 44	97 ± 40	0.08
Calories (kcal/kg)	69 ± 25	74 ± 28	72 ± 27	0.2
Amino acids (g/kg)	2.2 ± 0.9	2.3 ± 0.9	2.2 ± 0.9	0.2
Nitrogen (g/kg)	0.34 ± 0.1	0.36 ± 0.1	0.35 ± 0.1	0.2
Carbohydrates (g/kg)	12.9 ± 5.5	13.7 ± 5.9	13.4 ± 5.7	0.4
Lipid (g/kg)	2.3 ± 0.8, 0.5–3	2.2 ± 0.9, 0.5–3	2.2 ± 0.9, 0.5–3	0.9
Fat infusionsx7 per week[a]	64 (90%)	48 (86%)	112 (88%)	
Fat infusionsx3 per week	7 (10%)	7 (13%)	14 (11%)	
Fat infusionsx2 per week	—	1 (1%)	1 (1%)	
Complications				
CVC changes[a]	19 (27%)	14 (25%)	33 (26%)	0.2
Number of CVC changes[c]	0.90 ± 1.2	0.5 ± 1	0.7 ± 1	
CRBSI—number of affected cases	35 (49%)	34 (60%)	69 (54%)	0.2
CRBSI episodes/1000 CVC days[c]	15 ± 26	15 ± 69	15 ± 51	0.2
Outcome				
Enteral feeding[a]	51 (72%)	33 (59%)	84 (66%)	0.6
Home PN	14 (20%)	9 (16%)	23 (18%)	0.7
Death	6 (8%)	14 (25%)	20 (16%)	0.2
Related to PN	1 (17%)	2 (14%)	3 (15%)	
Related to underlying disease	5 (83%)	12 (86%)	17 (85%)	

Abbreviations: CRBSI, catheter-related bloodstream; CVC, central venous catheter; PN, parenteral nutrition. [a]Results are presented as number (% of total). [b]Results are presented as median (range); analyses by *t*-test. [c]Results are presented as mean ± s.d.; analyses by *t*-test.

Changes in high-risk groups

Hyperbilirubinaemia for ⩾2 weeks. Forty-four cases (20 SMOF and 24 Lipofundin) had hyperbilirubinaemia >50 μmol/l (⩾2.9 mg/dl) that persisted for ⩾2 weeks after commencing a new/mixed ILE (see Table 4 for details). Hyperbilirubinaemia persisted throughout the study period in 20 (6/20 SMOF and 14/24 Lipofundin, $P=0.02$). Eleven other cases developed hyperbilirubinaemia on treatment with a new/mixed ILE, that is, during the study period. Of a total of 31 children (20+11), 24% had hyperbilirubinaemia on discontinuing PN. Hyperbilirubinaemia incidence decreased from 44/127, 34% to 31/127 24% ($P\leqslant 0.05$). A similar proportion of hyperbilirubinaemic cases resolved with both ILEs, that is, 14 (20%) with SMOF and 10 (18%) with Lipofundin ($P=0.8$). Significantly fewer children receiving SMOF had persistent hyperbilirubinaemia on stopping PN compared with those on Lipofundin, that is, 10/71,14%, SMOF versus 21/56, 38% Lipofundin ($P=0.001$).

Four (36%) of the 11 patients who developed cholestasis while on treatment were male and seven (63%) were neonates. Median age was 0.7 (range 0.1–16) years. The underlying diagnosis was a primary digestive diagnosis in five (45%). Seven children developed cholestasis while on Lipofundin and in four treated with SMOF ($P=0.2$). Median duration of new ILE treatment was 29

Table 3. Effect of treatment on routine biological safety indexes

	SMOF			*Lipofundin*		
	Start	*End*	P-*value*	*Start*	*End*	P-*value*
Weight	10.6 ± 11.4	11.4 ± 10.6.	0.002	9.6 ± 8	10.4 ± 11.7	0.007
Albumin	27 ± 5	32 ± 6	< 0.001[a]	29 ± 6	33 ± 5	< 0.001[b]
ALP	440 ± 420	319 ± 192	0.008	497 ± 328	408 ± 361	0.05
ALT	169 ± 324	58 ± 56	0.006	197 ± 291	97 ± 100	0.01[b]
γ-GT	206 ± 284	166 ± 217	0.01	338 ± 613	246 ± 466	0.1
T bilirubin	69 ± 73	50 ± 115	0.1	91 ± 83	80 ± 126	0.6
C bilirubin	39 ± 59	33 ± 97	0.7	50 ± 65	50 ± 102	0.9
Triglycerides	2.7 ± 2.1	2.8 ± 0.3	0.2	2.7 ± 1.8	2.6 ± 2.2	0.1
Cholesterol	3.4 ± 2.1	2.8 ± 0	0.2	4.9 ± 2.25	5 ± 2.1	0.5
Prothrombin	11.9 ± 1.6	12 ± 3.0	0.3	13.3 ± 3.4	12 ± 1.7	0.1
Fibrinogen	2.6 ± 1.5	2.5 ± 1.1	0.6	2.8 ± 2.1	2.4 ± 0.9	0.3
Platelets	248 ± 162	238 ± 145	0.5	194 ± 113	241 ± 163	0.08
Leucocytes	11.6 ± 10.3	9.9 ± 5.2	0.2	12 ± 8.2	10 ± 8.9	0.2
CRP	46 ± 49	22 ± 38	0.02	35 ± 31	26 ± 31	0.2
Haemoglobin	9.8 ± 1.6	9.6 ± 1.2	0.4	9.4 ± 1.7	9.6 ± 1.5	0.3

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transferase; C, conjugated bilirubin; CRP, C-reactive protein; γ-GT, γ-glutamyl transferase; T, total bilirubin. Results are presented as mean ± s.d. *Analysis by paired t-test*. SMOF start vs SMOF end ($P \leqslant 0.05$). Lipofundin start vs Lipofundin end ($P \leqslant 0.05$). *Discontinuous analysis by Mann–Whitney U-test data analysis.* [a]SMOF start vs Lipofundin start, $P \leqslant 0.05$. [b]SMOF end vs Lipofundin end, $P \leqslant 0.05$.

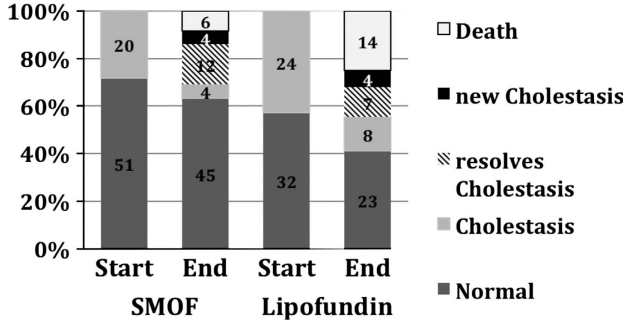

Figure 1. Changes in hyperbilirubinaemia in children with SMOF compared with Lipofundin.

(range 20–89) days, with a median total lipid of 2 g/kg per infusion (range 0.5–3). Soybean lipid component was 0.9 g/kg per infusion (range: 0.2–1.5).

Neonates and infants < 12 months. Overall liver enzyme levels decreased on treatment with both ILEs in neonates and infants. On stopping treatment, γ-GT levels were significantly lower with SMOF than Lipofundin ($P = 0.003$ neonates and $P = 0.02$ infants). Neonates also had lower ALP levels ($P = 0.004$) and infants had significantly lower ALT ($P = 0.002$), with SMOF compared with Lipofundin. Body weight and blood albumin significantly increased with both lipids ($P \leqslant 0.02$). Neonates treated with Lipofundin had significantly higher albumin on stopping PN than those given SMOF ($P = 0.002$).

Persistent IF >27 days. Seventy-nine children were treated with PN >27 days [32], 50 with SMOF and 29 Lipofundin. Twenty-three of 79, 29% had hyperbilirubinaemia on starting treatment, and in six, it developed while on treatment with a new ILE. In 16 of 23, the hyperbilirubinaemia resolved and in 7 it persisted. Six of 79 children developed hyperbilirubinaemia for the first time on a new/mixed ILE. There were no significant differences between the new ILEs when outcome was compared after several months on PN.

Twenty-three (18%) patients were discharged home on PN. None of the children underwent liver or small bowel transplant.

DISCUSSION

Both new ILEs were safe and well tolerated even in high-risk groups, such as children with hyperbilirubinaemia, neonates, premature infants and those on long-term PN >27 days.[26,27,34–36]

Patients improved nutritionally with significant weight gain (SMOF, $P = 0.002$; Lipofundin, $P = 0.007$) and reduced inflammation (CRP decrease with SMOF, $P = 0.02$; Lipofundin, $P = 0.2$) with both ILEs. There was a significant reduction in ALT and ALP with both SMOF ($P < 0.008$) and Lipofundin ($P < 0.05$), with additional significant reduction in γ-GT with SMOF. The incidence of hyperbilirubinaemia on discontinuing PN decreased from 34 to 24% ($P \leqslant 0.05$).

Both new ILEs appeared to have advantages over Intralipid and were associated with improved liver function. It is unclear as to what extent improvement was related to reduced soybean in the ILE and hence less accumulation of phytosterols and the proinflammatory effect of Ω-6 fatty acids, as well as inadequate provision of α-tocopherol[37] or to positive effects of the alternative lipid sources, MCT, olive or fish oil. Soybean lipid can reduce bile flow and hence potentiate cholestasis. In contrast, an animal study demonstrated that altering the fatty acid composition of ILEs by using fish oil reduces the severity of PN-induced cholestasis by preserving bile flow and composition by modifying hepatocyte membrane composition and function.[38]

Our data suggest that the additional olive and fish oil in SMOF might be more effective than adding MCT alone to soybean ILE in improving hyperbilirubinaemia, cholestasis and inflammation. Although MCT is a calorie-rich compound that lacks the disadvantages of soybean, it does not appear to have the potential anti-inflammatory effects of fish and olive oil. However, Lipofundin contains a higher proportion of soybean ILE than SMOF, that is, 10 g/100 ml as opposed to 6 g/100 ml in SMOF and this alone might account for some of the differences between the two new/mixed ILEs.

Significantly fewer children had persistent hyperbilirubinaemia with SMOF compared with the MCT/long-chain triglycerides ILE despite a similar proportion with each ILE receiving ursodeoxycholic acid. It was not possible to compare the benefit of fish with olive oil as the two were only given in combination. Further

Table 4. Significant effects of treatment on routine biological safety indexes in high-risk patients

	SMOF			*Lipofundin*		
	Start	*End*	P-value	*Start*	*End*	P-value
Parameter						
Children with total blood bilirubin level >50 μmol/						
Weight	4.8 ± 4.5	6 ± 5.6	0.01	7.7 ± 8.2	8 ± 7.9	0.1
Albumin	24 ± 4	31 ± 7	0.004	28 ± 6	33 ± 4	0.002
ALP	414 ± 258	346 ± 242	0.3	595 ± 336	392 ± 27	0.008
ALT	148 ± 169	69 ± 47	0.03	237 ± 388	97 ± 72	0.1
CRP	55 ± 34	11 ± 12	< 0.001	14 ± 10	11 ± 9	0.6
Neonates						
Weight	3.3 ± 0.9	4.3 ± 1.3	< 0.001	3.4 ± 0.4	3.8 ± 0.5	0.02
Albumin	25 ± 4	31 ± 5	< 0.001	26 ± 5	35 ± 5	< 0.001[b]
ALP	387 ± 216	365 ± 214	0.6	549 ± 233	390 ± 277	0.02[b]
ALT	115 ± 136	60 ± 43	0.04	74 ± 54	92 ± 70	0.3
Infants under 1 year of age						
Weight	4.3 ± 3.5	5.4 ± 4.4	< 0.001	4.7 ± 3	5.3 ± 2.9	0.07
Albumin	26 ± 5	32 ± 6	< 0.001[a]	28 ± 5	34 ± 5	< 0.001
ALP	456 ± 295	353 ± 204	0.03[a]	598 ± 322	472 ± 421	0.05
ALT	123 ± 133	50 ± 39	0.01	163 ± 158	118 ± 116	0.09[b]
γ-GT	162 ± 111	106 ± 78	0.1	357 ± 747	309 ± 567	0.5[b]
Children with long-term intestinal failure >27 days						
Weight	9.3 ± 9.3	10.2 ± 8.5	0.002	10.8 ± 9	12 ± 9	0.02
Albumin	33.6 ± 6	28 ± 6	< 0.001	34 ± 5	30 ± 6	0.06

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transferase; CRP, C-reactive protein; γ-GT, γ-glutamyl transferase. Results are presented as mean ± s.d. *Analysis by paired t-test*. SMOF start vs SMOF end ($P \leqslant 0.05$). Lipofundin start vs Lipofundin end ($P \leqslant 0.05$). *Discontinuous analysis by Mann–Whitney U-test data analysis*. [a]SMOF start vs Lipofundin start, $P \leqslant 0.05$. [b]SMOF end vs Lipofundin end, $P \leqslant 0.05$.

development and testing of fish and olive oil enriched ILEs and the impact on bile flow is needed.

The higher ratio of Ω-3:Ω-6 fatty acids in SMOF of 2.5:1 when compared with Lipofundin (approximately 1:7) would be expected to inhibit the secretion of the proinflammatory cytokines that may injure the liver.[5,26] There was a significant decrease in blood CRP level with SMOF when compared with Lipofundin that might also be attributed to the Ω-6: Ω-3 ratio. In addition, the Ω-9 content of olive oil has anti-inflammatory properties. Ω-9 decreases the risk of peroxidation and free radical production, which are potentially toxic to the cell membrane structure, circulating lipoproteins and the reticuloendothelial system.[39]

One possible disadvantage of fish oil is the lack of Ω-6 and that EFA deficiency might develop,[5] although this has not been evident in pure fish oil ILE studies.[21] None of the children in this study had clinical symptoms of EFA deficiency, but they were all given ILE that included soybean that contains Ω-6 EFAs.

The greater bioavailability and higher concentration of α-tocopherol in SMOF may also contribute to its benefits. Vitamin E is mainly in the γ-isoform in soybean ILE that is less bioavailable than the α-isoform.[26,40] Higher vitamin E levels with the higher α-tocopherol content of newer ILEs, such as SMOF and Lipofundin, might contribute to improved liver function.[26,40] The antioxidant effect of the higher vitamin E content could also have a positive anti-inflammatory effect.

There was a 35% (44 of 127 patients) incidence of hyperbilirubinaemia when the new ILEs were commenced with a similar distribution with each lipid. On completing treatment, fewer children had hyperbilirubinaemia with SMOF than with Lipofundin. The management strategy for prevention or treatment of IFALD when PN was still needed was usually to decrease or stop lipid infusion,[4] with the potential to affect adversely weight gain and growth. With new mixed ILEs, a new era of PN has begun in which it may be advantageous to continue administering ILEs in the presence of cholestasis/abnormal liver enzyme levels. A recent study suggested that introduction of fish oil earlier may also affect duration of cholestasis and indeed prevent cholestasis.[22]

Although overall the number of patients with hyperbilirubinaemia fell, 11 patients newly developed hyperbilirubinaemia whilst on treatment, 7 on Lipofundin and 4 on SMOF. The aetiology of newly acquired hyperbilirubinaemia might not be related to the ILE at all, but due to other factors such as concomitant administration of hepatotoxic drugs, such as chemotherapeutic medication. However, it is possible that even the lower concentration of soybean oil in mixed ILE formulations may predispose to liver disease in susceptible patients.

ILEs are a major source of non-protein energy.[41] Overall there was a significant increase in weight gain with both lipids. Adequate non-protein calorie intake facilitates effective protein metabolism reflected by a significant increase in albumin concentration with both new ILEs.

Premature neonates are at greatest risk of developing liver damage with PN.[1–3] Both new ILEs were well tolerated in neonates with a significant increase in albumin and weight gain achieved. With SMOF, there was additionally a significant decrease in ALT and lower ALP and γ-GT levels. New ILEs should be considered as the treatment of choice in neonates. In addition to reduced risk of liver disease, the higher ratio of Ω-3: Ω-6 would be expected to benefit neonatal neurological development and reduce inflammation. Long-term studies including outcome data are required to confirm these findings.

One limitation of this study was that it was retrospective. Second, the two new ILEs have different proportions of soybean ILE as discussed above. Another potential problem was that children with abnormal liver function at the start of treatment who had previously been given Intralipid were included. While initial abnormal liver function could be considered a limitation, we were able to demonstrate that pre-existing liver damage usually resolved with both ILEs. Third, Lipofundin was licensed and used routinely from 2006, whereas SMOF was licensed and used from 2009. It is possible that subtle changes in practice from 2006 to

2009 may have influenced outcome. However, three of the authors regularly performed nutrition rounds during the whole study period and were not aware of any significant changes in practice other than chlorhexidine introduction. The study was performed in children with a great variety of diseases and wide age range from neonates to 16 years that could have made it difficult to draw conclusions. However, these were the range of patients treated at the time of the study and are representative of the types of paediatric patients given PN in current clinical practice in a specialist children's hospital.31 Finally, blood transfusions can impact on liver function and bilirubin levels (data not shown).

CONCLUSION

Our data suggest that a mixed MCT and soybean ILE was an effective and safe alternative to pure soybean ILE. Less liver disease developed *de novo*, pre-existing liver disease acquired with a pure soybean ILE resolved, and albumin levels and weight gain improved. The addition of olive and fish oil to soybean, as well as MCT, was of even greater benefit with significantly lower incidence of cholestasis, significant improvement in γ-GT, less persistent hyperbilirubinaemia and significant reduction in CRP.

Mixed ILEs should be considered as first choice of treatment in patients at high risk of liver disease and those who may need PN for >27 days.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank all the professionals involved in the care of these complex patients including the nurses, dietitians, pharmacists, laboratory staff, medical teams and parents. No external funding was secured for this study.

AUTHOR CONTRIBUTIONS

JP has designed the data collection instruments, coordinated and supervised data collection, carried out the initial analyses, drafted the initial manuscript, critically reviewed the manuscript and approved the final manuscript as submitted. VS has designed the data collection instruments, critically reviewed the manuscript, and approved the final manuscript as submitted. SM critically reviewed the manuscript, and approved the final manuscript as submitted. SH conceptualised and designed the study, critically reviewed the manuscript and approved the final manuscript as submitted.

REFERENCES

1 Kelly DA. Preventing parenteral nutrition liver disease. *Early Hum Dev* 2010; **86**: 683–687.
2 de Meijer VE, Gura KM, Meisel JA, Le HD, Puder M. Parenteral fish oil monotherapy in the management of patients with parenteral nutrition-associated liver disease. *Arch Surg* 2010; **145**: 547–551 (review).
3 Beath SV, Davies P, Papadopoulou A, Khan AR, Buick RG, Corkery JJ *et al.* Parenteral nutrition-related cholestasis in postsurgical neonates: multivariate analysis of risk factors. *J Pediatr Surg* 1996; **31**: 604–606.
4 Colomb V, Goulet O, De Potter S, Ricour C. Liver disease associated with long-term parenteral nutrition in children. *Transplant Proc* 1994; **26**: 1467.
5 Goulet O, Joly F, Corriol O, Colomb-Jung V. Some new insights in intestinal failure-associated liver disease. *Curr Opin Organ Transplant* 2009; **14**: 256–261.
6 Diamond IR, Sterescu A, Pencharz PB, Wales PW. The rationale for the use of parenteral omega-3 lipids in children with short bowel syndrome and liver disease. *Pediatr Surg Int* 2008; **24**: 773–778.
7 Colomb V, Jobert-Giraud A, Lacaille F, Goulet O, Fournet JC, Ricour C. Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children. *J Parenter Enteral Nutr* 2000; **24**: 345–350.
8 Krohn K, Koletzko B. Parenteral lipid emulsions in paediatrics. *Curr Opin Clin Nutr Metab Care* 2006; **9**: 319–323.
9 Koletzko B, Goulet O. Fish oil containing intravenous lipid emulsions in parenteral nutrition-associated cholestatic liver disease. *Curr Opin Clin Nutr Metab Care* 2010; **13**: 321–326.
10 Schuberth O, Wretlind A. Intravenous infusion of fat emulsions, phosphatides and emulsifying agents. *Acta Chir Scand* 1961; **13**: S278–S284.
11 Calhoun AW, Sullivan JE. Omegaven for the treatment of parenteral nutrition associated liver disease: a case study. *J Ky Med Assoc* 2009; **107**: 55–57.
12 Clayton PTA, Bowron A, Mills KA, Massoud A, Casteels M, Milla PJ. Phytosterolemia in children with parenteral nutrition-associated cholestatic liver disease. *Gastroenterology* 1993; **105**: 1806–1813.
13 Clayton PT, Whitfield P, Iyer K. The role of phytosterols in the pathogenesis of liver complications of pediatric parenteral nutrition. *Nutrition* 1998; **14**: 158–164.
14 Tilley SL, Coffman TM, Koller BH. Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. *J Clin Invest* 2001; **108**: 15–23.
15 Wanten GJ, Calder PC. Immune modulation by parenteral lipid emulsions. *Am J Clin Nutr* 2007; **8 5**: 1171–1184.
16 Ekema G, Falchetti D, Boroni G, Tanca AR, Altana C, Righetti L *et al.* Reversal of severe parenteral nutrition-associated liver disease in an infant with short bowel syndrome using parenteral fish oil (omega-3 fatty acids). *J Pediatr Surg* 2008; **43**: 1191–1195.
17 Gura KM, Duggan CP, Collier SB, Jennings RW, Folkman J, Bistrian BR *et al.* Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. *Pediatrics* 2006; **118**: e197–e201.
18 de Meijer VE, Le HD, Meisel JA, Gura KM, Puder M. Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition-dependent patients. *J Pediatr Gastroenterol Nutr* 2010; **50**: 212–218.
19 Diamond IR, Pencharz PB, Wales PW. Omega-3 lipids for intestinal failure associated liver disease. *Semin Pediatr Surg* 2009; **18**: 239–245 (review).
20 Gura KM, Parsons SK, Bechard LJ, Henderson T, Dorsey M, Phipatanakul W *et al.* Use of a fish oil-based lipid emulsion to treat essential fatty acid deficiency in a soy allergic patient receiving parenteral nutrition. *Clin Nutr* 2005; **24**: 839–847.
21 Gura KM, Lee S, Valim C, Zhou J, Kim S, Modi BP *et al.* Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. *Pediatrics* 2008; **121**: e678–e686.
22 Le HD, de Meijer VE, Robinson EM, Zurakowski D, Potemkin AK, Arsenault DA *et al.* Parenteral fish-oil-based lipid emulsion improves fatty acid profiles and lipids in parenteral nutrition-dependent children. *Am J Clin Nutr* 2011; **94**: 749–758.
23 Park KT, Nespor C, Kerner J Jr. The use of Omegaven in treating parenteral nutrition-associated liver disease. *J Perinatol* 2011; **31**: S57–S60.
24 Puder M, Valim C, Meisel JA, Le HD, de Meijer VE, Robinson EM *et al.* Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. *Ann Surg* 2009; **250**: 395–402.
25 D'Ascenzo R, D'Egidio S, Angelini L, Bellagamba MP, Manna M, Pompilio A *et al.* Parenteral nutrition of preterm infants with a lipid emulsion containing 10% fish oil: effect on plasma lipids and long-chain polyunsaturated fatty acids. *J Pediatr* 2011; **159**: 33–38.
26 Goulet O, Antebi H, Wolf C, Talbotec C, Alcindor LG, Corriol O *et al.* A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish oil: a single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. *J Parenter Enteral Nutr* 2010; **34**: 485–495.
27 Mertes N, Grimm H, Fürst P, Stehle P. Safety and efficacy of a new parenteral lipid emulsion (SMOFlipid) in surgical patients: a randomized, double-blind, multicenter study. *Ann Nutr Metab* 2006; **50**: 253–259.
28 Rayyan M, Allegaert T, Devlieger H. Effect of a new type of lipid emulsion based on soybean oil, MCT, olive oil and fish oil (SMOF 20%) in preterm infants [abstract]. *Pediatr Crit Care Med* 2007; **8** (Suppl 3): A318.
29 Tomsits E, Pataki M, Tölgyesi A, Fekete G, Rischak K, Szollár L. Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil: a randomised, double-blind clinical trial in premature infants requiring parenteral nutrition. *J Pediatr Gastroenterol Nutr* 2010; **51**: 514–521.
30 Bishay M, Pichler J, Horn V, Macdonald S, Ellmer M, Eaton S *et al.* Intestinal failure-associated liver disease in surgical infants requiring long-term parenteral nutrition. *J Pediatr Surg* 2012; **47**: 359–362.
31 Pichler J, Horn V, Macdonald S, Hill S. Intestinal failure-associated liver disease in hospitalised children. *Arch Dis Child* 2012; **97**: 211–214.
32 Gowen H, Lloyd C. British Intestinal Failure Survey (BIFS): a referral registry to record and determine the outcome of childhood intestinal failure. *Proc Nutr Society* 2009; **68**: E15.

33 Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R *et al.* Parenteral Nutrition Guidelines Working Group, *et al*. 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr* 2005; **41**(Suppl 2): S1–S87.

34 Goulet O, Postaire M, De Potter S, Boya I, Jouniaux AM, Bereziat G *et al.* Medium-chain triglycerides and long-term parenteral nutrition in children. *Nutrition* 1992; **8**: 333–337.

35 Lai HS, Lin WH, Wu HC, Chang KJ, Chen WJ. Effects of a medium-chain triacylglycerol/long-chain triacylglycerol fat emulsion containing a reduced ratio of phospholipid to triacylglycerol in pediatric surgical patients. *Nutrition* 2005; **21**: 825–830.

36 Lehner F, Demmelmair H, Röschinger W, Decsi T, Szász M, Adamovich K *et al.* Metabolic effects of intravenous LCT or MCT/LCT lipid emulsions in preterm infants. *J Lipid Res* 2006; **47**: 404–411.

37 Diamond IR, Pencharz PB, Feldman BM, Ling SC, Moore AM, Wales PW. Novel lipid-based approaches to pediatric intestinal failure-associated liver disease. *Arch Pediatr Adolesc Med* 2012; **166**: 473–478.

38 Van Aerde JE, Duerksen DR, Gramlich L, Meddings JB, Chan G, Thomson AB, Clandinin MT. Intravenous fish oil emulsion attenuates total parenteral nutrition-induced cholestasis in newborn piglets. *Pediatr Res* 1999; **45**: 202–208.

39 Goulet O, de Potter S, Antébi H, Driss F, Colomb V, Béréziat G *et al.* Long-term efficacy and safety of a new olive oil-based intravenous fat emulsion in pediatric patients: a double-blind randomized study. *Am J Clin Nutr* 1999; **70**: 338–345.

40 Wanten G, Beunk J, Naber A, Swinkels D. Tocopherol isoforms in parenteral lipid emulsions and neutrophil activation. *Clin Nutr* **21**: 417–422.

41 Salas J, Girardet JP, De Potter S, Martí-Henneberg C, Goulet O, Ricour C. Glucose versus glucose-fat mixture in the course of total parenteral nutrition: effects on substrate utilisation and energy metabolism in malnourished children. *Clin Nutr* 1991; **10**: 272–278.