Influence of different intravenous lipid emulsions on fatty acid status and laboratory and clinical outcomes in adult patients receiving home parenteral nutrition: A systematic review

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Running title: Lipid emulsions in home parenteral nutrition

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Abstract

Background & aims: Intravenous lipid emulsions (IVLEs) are a key component in long-term home parenteral nutrition (HPN), providing energy and essential fatty acids (EFAs). Modification of the fatty acid (FA) composition of IVLEs may lead to changes in metabolic responses and cell and tissue function, providing opportunity for clinical improvements. Studies have suggested that, in place of conventional pure soybean oil (SO)-based IVLEs, which have a high omega-6 FA content, alternative IVLEs with different FA profiles may have beneficial effects. Our aim is to assess the effects of different IVLEs in adults dependent on HPN.

Methods: A systematic literature search using specific terms was performed up to December 2015. Randomised controlled trials (RCTs) comparing two or more IVLEs in adult patients receiving HPN were included. The Cochrane Collaboration's tool for assessing risk of bias was employed and data for outcomes of interest were extracted and collated for interpretation.

Results: Three RCTs met the eligibility criteria to be included in this review. Sample sizes ranged from 13 to 75, giving a total of 110 patients. All three RCTs reported similar clinical safety for alternative IVLEs compared to SO. Antioxidant status improved with SO-medium-chain triglyceride-olive oil-fish oil (SMOF) but not with olive oil-SO (OO-SO). There was no effect on inflammatory markers according to IVLE used. Phospholipid FA profile was modified by SMOF and OO-SO, with SMOF resulting in a more preferable omega-6/omega-3 FA ratio than SO. There was no evidence of essential fatty acid deficiency with any IVLE. Liver function was improved with SMOF.

Conclusions: There may be benefits in using alternative IVLEs rather than pure SO in adults on HPN, but there are currently too few RCTs to reach a firm conclusion.

Keywords: Home parenteral nutrition; intravenous lipid emulsion; soybean oil; olive oil; medium-chain triglyceride; fish oil

Abbreviations used: ALA, α-linolenic acid; ALT, alanine transaminase; AST, aspartate transaminase; CIF, chronic intestinal failure; DHA, docosahexaenoic acid; EFA, essential fatty acid; EPA, eicosapentaenoic acid; FA, fatty acid; FO, fish oil; γ-GT, gamma-glutamyl transpeptidase; HPN, home parenteral nutrition; IVLE, intravenous lipid emulsion; LA, linoleic acid; MCT, medium-chain triglyceride; OO, olive oil; PN, parenteral nutrition; PUFA, polyunsaturated fatty acid; SBS, short bowel syndrome; SMOF, soybean oil - medium chain triglyceride - olive oil - fish oil; SO, soybean oil.

1. Introduction

The delivery of nutrients by the intravenous route is referred to as parenteral nutrition (PN). Home parenteral nutrition (HPN) is recommended for patients who cannot meet their nutritional requirements by oral or enteral intake and who are able to receive PN outside of the acute care setting. Long-term HPN is indicated for patients with chronic intestinal failure (CIF); recently the European Society for Clinical Nutrition and Metabolism (ESPEN) endorsed recommendations in relation to the definition and classification of intestinal failure in adults [1]. Intestinal failure was defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth" [1]. Causes of CIF include obstruction, surgical resection, trauma, congenital defect, or disease-associated loss of absorption [1,2,3]. CIF is a disabling condition and may be associated with life-threatening complications. The most common indications for HPN in patients with CIF are short bowel syndrome (SBS), fistula, bowel dysmotility and radiation enteropathy [1,2,3]. Recently, ESPEN published guidelines on CIF in adults [3], having previously published guidelines on HPN in adults [2].

Patients receiving PN require a mixture of macro and micronutrients. Lipid is a very important component of PN because the fatty acid (FA) constituents are very good sources of energy. Indeed, intravenous lipid emulsions (IVLEs) were integrated into PN as a high energy source, reducing the need for high glucose infusion rates and, therefore, contributing to the prevention of hyperglycaemia and hepatic steatosis [2,4,5]. IVLEs are indispensable for the provision of essential fatty acids (EFAs). EFA deficiency is associated with numerous adverse effects including increased skin permeability, susceptibility to infection, impaired wound healing, hepatic fat infiltration, haematological disturbances and impaired fat absorption [6]. Without lipid, EFA deficiency develops within 2-6 months in patients on HPN [2,3].

Although HPN is a vital potentially life-saving treatment, there are inherent risks, with hepatic disorders being the most significant in terms of patients' prognosis [2,3,5]. The ESPEN guidelines recommend that around 15-30% of total energy intake should come from lipid, and exceeding this

has been shown to be an important factor in the development of chronic cholestasis and in progression to more severe liver disease [2,3]. A recent study found that two-thirds of patients on long-term HPN had persistent abnormalities in liver biochemistry [7], while another study reported a prevalence of complicated liver disease of 26% after two years of HPN [8].

Lipid emulsions contain a number of biologically active components, but the most important are FAs. Different FAs are metabolized by different pathways, exerting unique biological effects [9]. While saturated FAs serve primarily as an energy source, a number of polyunsaturated FAs (PUFAs) have important roles in the structure and function of membranes and serve as substrates for mediators that have roles in inflammation and immune responses, platelet aggregation and smooth-muscle contraction [9]. The simplest PUFAs of the omega-6 (n-6) family (linoleic acid (LA)) and of the n-3 family (α-linolenic acid (ALA)) cannot be synthesised de novo and are, therefore, referred to as EFAs.

There are a limited number of IVLEs available for use in HPN use, and all are based on the lipid sources soybean oil (SO), medium-chain triglycerides from coconut oil (MCT), olive oil (OO), and/or fish oil (FO) [10]. Table 1 summarises the compositions of the IVLEs that have been used in randomized controlled trials (RCTs) in adults on HPN. The traditional IVLE used in HPN is based solely on SO, meeting energy and EFA requirements. However, there are indications that mixtures of different oils result in a more favourable FA composition, which may translate into better laboratory and clinical outcomes for patients receiving HPN. The purpose of this systematic review is to assess the impact of the currently available IVLEs in adult patients receiving HPN.

2. Methodology

2.1 Literature search

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analyses (PRISMA) [11]. A systematic literature search of the Ovid MEDLINE(R) without Revisions (1996 to November 2015), EMBASE (Classic+Embase 1947 to December 2015) and CINAHL (up to November 2015) databases was performed to source relevant articles using both Free Text and Mesh terms based on the key terms “home parenteral nutrition” and “intravenous lipid emulsions”. All searches were conducted between September and December 2015. The limits *Humans* and *English Language* were applied. There were no restrictions on the searches for population or year of publication. Supplementary Table 1 shows the search strategy carried out using MEDLINE. Reference lists of previous reviews and reference lists of retrieved articles were also manually searched, but these did not yield any additional studies that were not already identified through the electronic search.

2.2 Study selection

The eligibility of studies to be included in the systematic review was assessed using the following criteria: primary research comparing two or more IVLEs; all participants dependent on HPN; participants aged 18 years or above; randomised controlled trial (RCT) study design, and published in the English language. Studies were excluded if there was no reference to whether parenteral nutrition was administered at home or if published as abstracts, commentaries, case reports or conference proceedings.

Using the inclusion and exclusion criteria, the vast majority of articles were rejected on the basis of the title or abstract. If the abstract met the eligibility criteria, the full text article was retrieved for further assessment. All studies were reviewed by two reviewers (the authors) using the selection criteria to determine inclusion in the review.

2.3 Publication bias

Minimisation of publication bias was achieved by using a comprehensive search strategy involving

electronic databases as well as manual reference searches. However, a degree of bias may have occurred as a result of limiting the search to papers in the English language. Also, this search strategy did not allow for inclusion of studies that have not yet been published on electronic databases.

2.4 Data extraction

The following data were extracted from the full-text articles of all included studies: first author, publication year, study design, study location, study period, sample size, study population, inclusion and exclusion criteria, duration of HPN treatment (stage), type of treatment (IVLE), methods, outcomes measured, prevalence of adverse events and statistical analysis used. Differences in data interpretation were resolved by discussion between the authors.

2.5 Quality assessment

Study quality was assessed using the Cochrane Risk of Bias Tool [12].

3. Results

3.1 Search results

The electronic literature search yielded 3568 citations and no additional citations were identified through the manual searching of reference lists. Of these, 241 were duplicates and a further 3320 were excluded due to failure of the abstract to meet the eligibility criteria. Five prospective cohort and seven case studies met all eligibility criteria except study design, being non-RCTs, and so were not included in the review. Seven full text articles were examined, but on further inspection two did not exclusively include participants dependent on long-term HPN, one was not an RCT and one did not compare two different IVLEs. A final sample of three RCTs was included (Figure 1).

3.2 Characteristics of included trials

Table 2 shows the characteristics of the included trials. All three double-blind RCTs compared one alternative IVLE to a pure SO-based IVLE using two groups of patients with comparable demographics. One RCT had a cross-over design with each participant receiving both interventions [13]. The emulsions used were SMOFLipid 20% (SO/MCT/OO/FO; SMOF) [14], ClinOleic 20% (OO-SO) [15] and Structolipid 20% (structured SO-MCT (SO-MCT)) [13]. One RCT was a multi-center study (involving 11 centers in 7 countries) [14], whereas the other two were single-center studies.

All three RCTs enrolled adults with a variety of long-term gastro-intestinal conditions, although the most frequent indication for HPN across all studies was SBS or Crohn's Disease. The average age of patients was also similar across all studies (between 40 and 55 years). The sample sizes were small; the number of patients that received the allocated intervention – the intention to treat (ITT) population – was 20, 13 and 73 respectively, although data for the latter study were only analysed for 62 patients. There was an unclear risk of bias for at least one category for each RCT; a common weakness was absent reporting with regards to blinding of outcome assessors (detection bias) and incomplete data (attrition bias) in two RCTs (see Table 3).

The average duration of HPN therapy prior to the study period was similar for the two RCTs that reported these data, and was also similar between the two groups assigned different interventions within the studies, the average being around 5 to 6 years [13,15]. Study duration was one [13,14] or three [15] months. All three RCTs reported laboratory parameters for liver function as a primary outcome. Two RCTs reported the FA profile in plasma and/or red blood cell membrane phospholipids [14,15] and two RCTs reported inflammatory and/or lipid peroxidation markers [13,14]. Table 4 summarises the main results of the RCTs.

3.3 Effect of intervention on liver function

With the exception of two patients that showed significantly abnormal concentrations of liver enzymes after receiving the SO-based IVLE [13], none of the RCTs found any impairment in liver function with either the SO-based or the alternative IVLE. Mean concentrations of alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin were significantly lower in patients who received SMOF (p=0.049, 0.027 and 0.043, respectively) at the end of, compared with the beginning, of the treatment period [14]. In contrast, liver function test changes from the start to the end of the study were not different between the OO-SO and SO groups [15]. However, when the two patients in the cross-over study that developed significantly increased liver enzyme concentrations with the SO-based emulsion were switched to the structured SO-MCT IVLE, liver biochemical markers returned to normal ranges [13].

3.4 Effect of intervention on fatty acid profile

The change in FA profile in plasma phospholipids over the three month study period was significantly different between the SO and OO-SO groups for oleic acid (p=0·01), gamma-linolenic acid (p=0·02), and mead acid (n-9 eicosatrienoic acid) (p=0·04), which all increased with OO-SO [15]. The difference between the two groups for change in gamma-linolenic acid over the study period (day 0-90) was significant in lymphocyte membranes (p=0.02) as well as in plasma

phospholipids [15]. Additionally, there was a significant decrease for gamma-linolenic acid in lymphocytes in the SO group (p=0·03). There was a significant correlation between daily parenteral intake of LA and change in gamma-linolenic acid in plasma phospholipids (p=0·009) with a non-significant trend seen in lymphocytes (P=0·13).

Excluding samples with identified lipid peroxidation (giving a reduced sample size of 14 for the SMOF group and 20 for the SO group), EPA and DHA in both plasma and erythrocytes increased in the SMOF group [14]. This difference was significant for change from baseline to week 4 in the SMOF group and between SO and SMOF groups at end of study (week 4). Consequently, the n-6/n-3 fatty acid ratio was significantly lower at the end of the treatment period in patients who received SMOF compared to those who received SO (p<0.0001 for plasma and p=0.003 for erythrocytes) [14]. SMOF did not affect arachidonic acid in either plasma or erythrocytes [14].

The triene:tetraene ratio, indicating EFA deficiency, was only reported in one study [15] and was below the threshold of 0·2 for both the SO and SO-OO groups. There was no clinical evidence of EFA deficiency in any of the study periods.

3.4 Effect of intervention on inflammatory status

Two studies reported inflammatory markers in plasma [14,15]. Interleukin-6, soluble tumour necrosis factor receptor II and C-reactive protein concentrations remained 2-3 times above reference values from baseline in both the SO and SMOF groups until the end of the study and did not differ between the two groups [14]. Any change in C-reactive protein was not different between the OO-SO and SO groups [15].

3.4 Effect of intervention on antioxidant status

Serum α-tocopherol (vitamin E) levels, indicating antioxidant status, were significantly increased in patients receiving SMOF compared to those receiving SO at both week 2 and 4 (endpoint of study) ($p<0.05$) [14], whereas the change was not statistically different between the SO-OO and SO groups over the 90-day study period [15]. Plasma dicarboxylic acids and 3-hydroxy FAs were similar with either SO or structured SO-MCT [13].

3.4 Adverse events

In terms of clinical safety and tolerance, all three alternative IVLEs showed similar results to that of SO. In one study, five patients in the structured SO-MCT group experienced vomiting and one patient developed skin desquamation while four patients in the SO group also experienced vomiting [13]. It was considered unlikely that any adverse events (AEs) were related to the treatment, and all patients recovered without disruption to the course of treatment. No significant AEs occurred in the SO-OO group and one acute pneumonia episode occurred in the control group, but again with no disruption to the treatment course [15].

31 AEs in 15 patients (44.1%) who received SMOF were reported compared to 51 AEs in 21 patients (53.8%) receiving SO ($p = 0.11$) [14]. In the SMOF group, two AEs in two patients were classed as serious (according to Common Terminology Criteria for AEs). Ten serious AEs in eight patients occurred in the SO group ($p=0.03$). Full recovery was reported for all cases. AEs accounted for discontinuation of the study treatment for two SMOF patients and six SO patients, with five AEs in two SMOF patients and six AEs in three SO patients ($p=1.000$) assessed as being possibly or probably related to the treatment, although none of these was serious.

4. Discussion

The inclusion criteria specified that only RCTs be included in this systematic review. This had the advantages of minimising the chance of bias in the results, with RCTs being the 'gold standard, and introducing consistency into the comparison of studies. However, a limitation was that this required exclusion of a large number of trials due to their study design i.e. they were not RCTs. In addition, each of the three included RCTs used SO as the control, which was useful in terms of producing comparable results but it would also be useful to directly compare one alternative emulsion against another in order to better quantify the effect. One RCT used a crossover design in which each patient acted as their own control.

Findings of two RCTs [14,15] support the hypothesis that effects of IVLEs on the FA profiles of plasma and cell membranes depend on, and are consistent with, the FA content of the IVLE. Although the finding was not significant in the RCT [15], other studies [16-20] on SO have found an association between an increase in LA exposure and an increase in arachidonic acid in phospholipids. This suggests that SO can promote the elongation and desaturation of LA to the pro-inflammatory arachidonic acid. However, one randomised crossover study in five adults found an increase in erythrocyte LA and decrease in arachidonic acid with SO [21], so the evidence is not consistent.

The RCT investigating the structured SO-MCT did not report FA profile as an outcome but some of the other studies of the replacement of SO with SO-MCT emulsions have reported no difference in PUFA levels with respect to baseline or compared between the IVLEs [22]. An RCT comparing SO to OO-SO in children [23] also observed that OO-SO use was associated with an increase in oleic acid and decrease in LA in both plasma and cell membrane phospholipids supporting the findings reported here in adults [15]. However, a non-randomised study evaluating the effects of OO-SO in adults receiving HPN over three months found that the only significant change with OO-SO was a decrease in ALA in plasma phospholipids [24]. This study and another 6-month crossover study in

adults on HPN [25] had consistent results regarding clinical safety and efficacy, finding that OO-SO was well-tolerated, maintained a normal EFA status, and did not affect liver function. This is a common finding.

An investigation of the effects of OO-based IVLEs on liver function found the OO-SO IVLE preserved liver markers more effectively [26] but this was not in an HPN population. Furthermore, a study in patients with HPN-associated liver disease found liver enzymes to be significantly improved after treatment with an OO-based IVLE [27]. Overall, these findings suggest that, in a metabolically stressed state, OO-SO may be preferable to SO in terms of improving liver function, although the evidence for this in the adult HPN population is not strong.

There is a shortage of studies that have looked at inflammatory and peroxidation indices and α-tocopherol status as outcomes with OO-SO emulsions, although an RCT in children reported lower lipid peroxidation with OO-SO [23]. The 3-month study period of the RCT in adults [15] may not have been sufficiently long enough to observe any significant change in these markers. Although OO-based IVLEs have been suggested as an alternative to SO in long-term HPN, the evidence is not sufficient to suggest that OO-SO is superior to traditional SO-based IVLEs in adults.

A significant and potentially clinically important finding was that treatment with SMOF led to an increase in the concentration of the very long-chain n-3 FAs, EPA and DHA, both of which have been strongly associated with beneficial biological and physiological effects [9]. The increased n-3:n-6 fatty acid ratio in plasma and cell membranes has also been found in an RCT in children [28]. SMOF had the additional benefits of positively affecting ALT, AST, and total bilirubin, as well as antioxidant status (alpha-tocopherol concentration). An increased concentration of n-3 PUFAs associated with a significant decrease in arachidonic acid was found in a prospective study in 15 adults investigating the treatment of liver disease in HPN patients with fish oil [29] and in a case study [30].

The findings of this systematic review may be considered in the context of the most recent ESPEN guidelines on CIF in adults [3]. The guidelines suggest “in patients totally dependent on HPN, a minimal supply of 1 g/kg/week of intravenous lipid emulsion containing EFA, to prevent EFA deficiency” [3]. The studies included in the current systematic review indicate that use of SO, SO-MCT, OO-SO or SMOF is appropriate for avoidance of EFA deficiency in adults on HPN. In the context of liver disease, the guidelines suggest “that most patients on long-term HPN for CIF without ongoing metabolic complications be safely treated with provision of no more than 1 g/kg/day of intravenous soybean-based lipid emulsion” [3]. Further, the guidelines recommend “for prevention of intestinal failure associated liver disease that …….the dose of soybean-oil based lipid is limited to less than 1 g/kg/day” and suggest “for treatment of intestinal failure-associated liver disease .... to revise the lipid component of the PN admixture, in order to decrease the total amount and/or to decrease the n-6/n-3 PUFA ratio” [3]. One study included in this systematic review [14] indicates that SMOF, which has a lower n-6 to n-3 fatty acid ratio than the other IVLEs considered here, may result in better liver function than SO-based IVLEs, but more studies are needed in this area.

5. Conclusion

Although the duration of the included studies was short, significant differences were found between SO and the alternative IVLEs. The RCTs did not produce any statistically significant differences in liver function tests between SO and alternative IVLEs, but SMOF appeared to improve liver function. The alternative IVLEs may exert clinical benefit long-term as indicated by the improved antioxidant status and FA profiles. Without more clinical data from RCTs of a longer duration, this cannot be determined. Prospective studies over a number of years would give a better indication of the long-term effects. Hence, larger and longer studies are needed, specifically in adults dependent on long-term HPN in order to determine whether one alternative IVLE is more effective in improving patient outcomes.

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Conflict of Interest

PCC has advised Fresenius-Kabi, B. Braun and Baxter Healthcare on the science of IVLEs. CJJ has no conflicts to report.

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Table 1

Summary of the composition of intravenous lipid emulsions used in RCTs in adults on HPN[1]

Lipid emulsion	SO	Structured SO-MCT	OO-SO	SMOF
Trade name	Intralipid	Structolipid	Clinoleic	SMOFLipid
Lipid Source (% by weight)	SO (100)	SO/MCT (64:36)	OO/SO (80:20)	SO/MCT/OO/FO (30:30:25:15)
LA (% of total FAs)	53	35	18.7	37.2
ALA (% of total FAs)	8	5	2.3	4.7
EPA + DHA (% of total FAs)	-	-	0.5	9.1
Oleic acid (% of total FAs)	24	14	62.3	55.3
Ratio of n-6 to n-3 PUFAs	7:1	7:1	9:1	2.5:1
α-tocopherol (mg/L)	38	~85	32	150 to 300
Phytosterols (mg/L)	~440	~350	~270	~50

[1] Data are taken from reference [10]

427 **Table 2**

428 Characteristics of the three included studies

Reference	IVLEs used	Sample size (a/b)[¶]	Sex (M/F)	Mean age (y)	Mean duration of HPN prior to study (months)	Exposure to intervention (months)	Indication for HPN
Rubin et al. 2000 [13]	SO-MCT then SO	10/9	7/3	40.8	53	2 (1 per IVLE)	SBS (n = 4) Crohn's (n = 4) Other (n = 2)
	SO then SO-MCT	12/11	7/5	45.3	60	2 (1 per IVLE)	SBS (n = 4) Crohn's (n = 8)
Vahedi et al. 2005 [15]	OO-SO	6/6	4/2	48.0	69	3*	SBS (n = 6)
	SO	7/7	1/6	53.0	77	3*	SBS (n = 4) Chronic intestinal pseudo-obstruction (n = 3)
Klek et al. 2013 [14]	SMOF	35/30	20/14	53.2	NR	1	SBS (n = 22) Crohn's (n = 5) Other (n = 8)
	SO	40/32	21/18	45.2	NR	1	SBS (n = 17) Crohn's (n = 3) Malabsorption (n = 5) Other (n = 6)

429

430 *(+ 1 month run-in period with MCT-SO); [¶]a) Number of patients randomised; [¶]b) Number of patients

431 that received allocated intervention and completed whole study duration.

Table 3

Bias table based on Cochrane Tool for assessing bias

Reference	Vahedi et al. 2005 [15]		Rubin et al. 2000 [13]		Klek et al. 2013 [14]	
Random sequence generation (selection bias)		Randomisation list based on a blocking method prepared by third party		Patient number in the randomization list generated in SAS code using the RANUNI procedure		Randomisation performed by means of electronic data processing using a seed depending random number generator
Allocation concealment (selection bias)		Performed by hospital pharmacist using numbered, sealed envelopes.		"The Department of Drug Supply used the information from the randomization list when labelling the fat-emulsion bottles"		"allocation to treatment groups was not known to the investigators until the completion of the study"
Blinding of participants and personnel (performance bias)		Double-blind		Double-blind		Double-blind
Blinding of outcome assessment (detection bias)		Not reported		Not reported		Not reported
Incomplete outcome data (attrition bias)		Insufficient reporting of attrition – no reasons given for reduced sample size in results tables		Reasons given for 2 withdrawals		Patients with lipid peroxidation not included in results table
Selective reporting (reporting bias)		Exclusion of data occurred				Exclusion of data occurred

435 **Table 4**

436 Summary of results from the three included studies

Reference	Study details	IVLEs used	Liver function tests	Inflammation and peroxidation indices	Clinical outcomes
Rubin et al. 2000 [13]	RCT, adults, n=22, 4 weeks	SO vs structured SO-MCT	SO: ALP, ALT, AST & γ-GT abnormal in 2 patients	Similar lipid peroxidation	Similar clinical safety and AEs (Vomiting n=5 for SO-MCT, n=4 for SO).
Vahedi et al. 2005 [15]	RCT, adults, n=13, 3 months	SO vs OO-SO	No differences	No change or difference in C-reactive protein	Similar AEs
Klek et al. 2013 [14]	RCT, adults, n=75, 4 weeks	SO vs SMOF	Normal but ALT, AST & total bilirubin lower with SMOF (p=0.049, 0.027 and 0.043)	Increase in serum α-tocopherol with SMOF (p<0.05) No change or difference in IL-6, sTNF-RII or C-reactive protein	Serious AEs more frequent with SO (p=0.03)

437 ALP = alkaline phosphatase, γ-GT = gamma glutamyl transpeptidase, AST = aspartate

438 transaminase, IL-6 = interleukin-6, sTNF-RII = soluble tumour necrosis factor receptor II

Supplementary Table 1

The Search Strategy using Combined Free Text and Mesh Terms in the Ovid Medline Database

1	exp Fat Emulsions, Intravenous/	1738
2	exp Parenteral Nutrition/	8011
3	(IVLE* or soy* oil or olive oil or fish oil* or MCT or lipid emuls* or lipid admixture or triacylgyceride* or triglyceride* or fatty acid* or fat emuls* or clinoleic* or intralipid* or ivelip* or lipoven* or lipofundin* or liposyn* or structolipid* or omegaven* or lipoplus* or lipidem* or SMOFlipid* or intrafat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	177217
4	((intravenous* adj6 feed*) or (intravenous* adj6 nutri*) or (IV adj6 nutri*) or (IV adj6 feed*) or (intravenous* adj6 fed) or (parenteral* adj6 fed) or (IV adj6 fed) or PN or HTPN or TPN or HPN or (parenteral* adj6 nutri*) or (parenteral* adj6 infusion*) or (parenteral* adj6 solution*) or (parenteral* adj6 admixture*) or (nutri* adj6 admixture*) or (intravenous* adj6 admixture*) or (IV adj6 admixture*) or nutrition* support).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	30359
5	1 or 3	177217
6	2 or 4	30359
7	5 and 6	1961

8	limit 7 to english language	1755
9	limit 8 to humans	1323

441

Figure 1

PRISMA flow diagram showing multistage search strategy and study selection