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

Samir Ahmed[a] Jacqueline K. Innes[a] and Philip C. Calder[a,b,*]

[a] School of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton SO16 6YD, United Kingdom

[b] National Institute for Health Research Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton SO16 6YD, United Kingdom

Running title: Lipid emulsions in home parenteral nutrition

*Corresponding author: Philip C. Calder, School of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton SO16 6YD, United Kingdom

Email: pcc@soton.ac.uk

Phone: +44 23281 205250

Abstract

Background & aims: Patients who have chronic intestinal failure require home parenteral nutrition (HPN) support. Intravenous lipid emulsions (IVLEs) are a vital part of HPN. The conventional IVLE is based on pure soybean oil, which contains a high concentration of omega-6 fatty acids. Alternative IVLEs are commercially available. These contain various oil blends and have different fatty acid compositions from soybean oil that could provide benefit to patients on HPN. The aim of this systematic review is to assess the effects of different IVLEs in adult patients requiring HPN.

Methods: A systematic literature search was conducted up to October 2019 using relevant search terms in the Medline, EMBASE and CINAHL databases. Only randomised controlled trials (RCTs) in adults on HPN that compared two or more IVLEs were included. Data were extracted and the Cochrane Collaboration's tool for assessing risk of bias was used.

Results: Six articles were identified for inclusion in this systematic review. Studies differed according to sample size, duration and the IVLEs compared. Four studies found no increased risk of adverse effects related to the different IVLEs, whilst one study found a higher frequency of serious adverse events with soybean oil. One study found higher serum α-tocopherol with the blend of soybean oil, medium chain triglycerides, olive oil and fish oil. Inflammatory markers were not affected by different IVLEs in three studies. Differences in liver function tests were minimal, but one study found slight abnormalities in patients receiving soybean oil. IVLEs containing olive oil or fish oil modified the blood fatty acid profile. No studies reported essential fatty acid deficiency.

Conclusions: There may be benefits of using alternative IVLEs to soybean oil-based emulsions in adults requiring HPN, although there is currently insufficient evidence to determine superiority of one formulation over another. More and larger RCTs are required in this area.

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

Abbreviations used: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CIF, chronic intestinal failure; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EFA, essential fatty acid; EPA, eicosapentaenoic acid; FO, fish oil; γ-GT, gamma-glutamyltransferase; HPN, home parenteral nutrition; IVLE, intravenous lipid emulsion; LE, lipid emulsion; 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

Parenteral nutrition (PN) refers to the intravenous administration of an aqueous formulation of nutrients. PN can be used for short term nutrition support (e.g. post-surgery) or for long term, even lifetime nutrition support. In the latter case PN can be administered by patients at home, referred to as home PN (HPN) [1]. HPN is generally administered overnight for a period of 12 hours and repeated between two and seven times a week, depending on the patient's remaining gut function [1].

Patients require HPN as a result of chronic intestinal failure (CIF) [2,3]. Intestinal failure is 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" [2]. CIF has many causes, which can include surgical removal of part of the intestine, trauma, obstruction, congenital defects or a disease which impairs nutrient absorption from the intestine. More often than not, patients who present with diseases such as short bowel syndrome (SBS), fistula, bowel dysmotility and radiation enteropathy are put onto HPN in order to provide them with adequate nutrition [3,4].

By definition, HPN should provide a full mix of nutrients including carbohydrates, fat, amino acids, vitamins and minerals [4]. The fat (or lipid) is present as an emulsion (lipid emulsion; LE). The reason for the inclusion of lipids in HPN is that they provide a source of energy and supply the body with essential fatty acids (EFAs) that are required for proper function. Since fatty acids can supply a large amount of energy, LEs lessen the need to infuse large amounts of glucose to meet the energy demands of the patient receiving HPN. A high glucose infusion can lead to complications, such as hyperglycaemia and hepatic steatosis. It is imperative that intravenous LEs (IVLEs) contain EFAs as deficiency can result in impaired wound healing, increased susceptibility to infection and haematological disturbances [5]. Other components of the LE include phospholipids, sterols and fat-soluble vitamins. Several LEs for use in HPN are commercially available. The standard LE (e.g. Intralipid) is based solely on soybean oil (SO). SO is rich in linoleic acid, an omega-6 (n-6) polyunsaturated fatty acid (PUFA), and also contains some alpha-linolenic acid, an omega-3 (n-3) PUFA. The high content of linoleic acid in SO has raised concerns about increased lipid peroxidation and inflammation [6] Oxidative stress and inflammation can play a role in the development of parenteral nutrition-associated liver disease [7]. As a result of these concerns, other LEs have been developed which retain SO as the base but utilise additional lipids such as olive oil (OO), medium chain triglycerides (MCT) and fish oil (FO) (see Table 1). As different fatty acids have varying functional effects [8], the different LEs could potentially influence metabolism, inflammation and oxidative stress in different ways.

A systematic review was published in 2018 to assess the impact of currently available IVLEs in adult patients receiving HPN [9] This review, based on a literature search conducted in November 2015, identified only three RCTs for inclusion which compared SO alone with SO-MCT [10], SO-OO

(ClinOleic) [11] or SO-MCT-OO-FO (SMOF; SMOFLipid) [12]. It is likely that new studies have since been published. Hence, the aim of this current systematic review is to provide an updated assessment of the effect of different IVLEs in adult HPN.

2. Methodology

2.1 Literature search

This study was designed and conducted in accordance with the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analyses (PRISMA) [13]. The following databases were searched for relevant literature: Ovid MEDLINE (from 1996 to October 2019), EMBASE (1947 to October 2019) and CINAHL (up to October 2019). Free text and Mesh searches using the terms 'home parenteral nutrition' and 'intravenous lipid emulsion' was performed. Additional search terms included intradialytic nutrition, intravenous feeding, peripheral parenteral nutrition, total parenteral nutrition, edible oil, lipid emulsion, olive oil, fish oil and soybean.

2.2 Study selection

Studies were selected for this systematic review on the basis of the following inclusion criteria: the study must have been primary research, used a randomised controlled trial study design, compared two or more LEs, included patients of age 18 years or over, included patients dependent on HPN and been published in the English language.

It was common to find research papers that did not specify whether PN was done in the home setting or where the age of the patients under investigation was not provided. Due to the chance that these articles may breach the inclusion / exclusion criteria, they were not included in the review. Other types of literature such as case reports, conference reports and articles that did not have an accessible full-text were also not included.

2.3 Publication bias

Minimisation of publication bias was achieved using a comprehensive search strategy involving electronic databases as well as manual reference searches.

2.4 Data extraction

Data from studies that met the inclusion criteria were extracted and included patient information such as mean age, sex, sample size, mean duration of HPN prior to study, time exposed to the intervention and reasons for needing HPN, as well as intervention information such as the different IVLEs compared, liver function test results, inflammation and peroxidation status and clinical outcomes.

2.5 Quality assessment

The quality of the studies included in the systematic review was assessed for bias using the

Cochrane Risk of Bias Tool [14].

3. Results

3.1 Search results

The electronic database search resulted in a total of 3,889 articles with no additional articles found using manual methods of searching. Of these, 109 duplicates were removed leaving a total of 3780 articles. A further 3,750 articles were removed due to not meeting the eligibility criteria. From the 30 remaining articles, 14 did not specify that PN was done at home, 8 did not specify if the trial was a randomised controlled trial, one referred to paediatric and not adult patients, and one did not compare two different IVLEs. Thus, 6 RCTs were eligible for inclusion in this systematic review [10,11,12,15,16,17] (Figure 1).

3.2 Characteristics of included trials

Key characteristics of the included trials are presented in Table 2. Five trials compared SO IVLE with alternative IVLEs such as SO-MCT [16,17], structured SO-MCT [10], SO-OO [11,16] and SMOF [12,16], whilst one trial compared SO-MCT with SO-MCT-FO [15]. Study duration varied ranging from 1 month [10,12] to 12 months [16] with one study of 2 months [15] and two studies of 3 months [11,17]. Sample size per IVLE group was typically quite small, ranging from 5 [17] to 32 [12] patients. All six studies enrolled patients with a wide variety of chronic intestinal conditions that warranted HPN support. Amongst the most common conditions were Crohn's disease, chronic intestinal failure due to vascular causes, inflammatory bowel disease and SBS. The average age of patients included in the six studies was comparable.

Two of the studies reported a similar mean duration of HPN prior to study inception and both managed to maintain a similar duration between the groups that were assigned to the different interventions; the average for these two studies was between 5 and 6 years [10,11]. One of the studies had a mean duration of HPN prior to study of between 22 to 25 days; this was the case for all four groups that participated in that study [16]. Three studies [12,15,17] did not record mean duration of HPN prior to study commencement.

There was an unclear risk of bias for at least one category for each study (Table 3). Not reporting blinding of outcome assessment was common to all studies. Method of randomization was not reported in two studies [16,17]. Four studies did not provide reasons for loss of follow-up [11,12,15,16] and three did not report data for all outcomes for all patients [11,12,15].

3.4 Effect of IVLEs on fatty acid profile

The main outcome in the study of Dahlan et al. [17] was the fatty acid profile of erythrocytes. They identified that daily infusion of a SO lipid emulsion for 3 months resulted in an increase in linoleic acid and a decrease in arachidonic acid in erythrocytes. DHA was decreased and there was a

tendency to decrease EPA. In contrast, SO-MCT given daily for 3 months induced no significant alteration in erythrocyte fatty acids. Because of the cross-over design of this study, the authors were able to demonstrate that SO-MCT reversed the changes induced by prior SO infusion.

Vahedi et al. [11] reported on plasma and blood lymphocyte fatty acids before and after 3 months of daily infusion of SO or SO-OO. SO-OO resulted in higher plasma oleic, γ-linolenic and mead acid than in the SO group. Mead acid is an indicator of EFA deficiency, but the triene:tetraene ratio (ratio of mead to arachidonic acid) remained lower than 0·2, the cutoff taken to indicate EFA deficiency, in all patients. As seen in plasma, lymphocyte γ-linolenic acid decreased in the SO group.

Klek et al. [12] reported fatty acids in plasma and erythrocytes before and after 4 wk daily infusion of SO or SMOF. SO increased plasma linoleic acid and decreased plasma oleic acid, SMOF increased plasma EPA and DHA. At the end of the infusion plasma EPA, docosapentaenoic acid (DPA) and DHA were higher and linoleic acid was lower in the SMOF group compared to the SO group. Changes in erythrocytes were of smaller magnitude but SMOF increased EPA and DHA and these fatty acids were higher after SMOF than after SO. SMOF did not alter plasma or erythrocyte arachidonic acid. The fatty acid composition of erythrocytes, platelets and serum phospholipids was significantly altered after 8 weeks of daily administration of SO-MCT-FO [15]. EPA, DPA and DHA increased while linoleic, γ-linolenic, dihomo-γ-linolenic and arachidonic acids decreased in erythrocytes, platelets and serum phospholipids. In the group receiving SO-MCT, fatty acids remained mostly stable.

3.3 Effect of IVLEs on markers of liver function

Few differences in markers of liver function have been reported with the different IVLEs (Table 4). Rubin et al. [10] observed that two patients had abnormal levels of alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST) and gamma-glutamyltransferase (γ-GT) after receiving the pure SO IVLE for 4 wk. These abnormal liver function markers returned to the normal range as soon as both these patients were switched to SO-MCT. Klek et al. [12] found that the mean concentrations of ALT, AST and total bilirubin were significantly lower in patients on 4 wk SMOF treatment than on pure SO. This effect was not replicated in a later study where the IVLEs were tested over 12 months [16]. In that study effects of SO-MCT and SMOF on liver function markers were not observed, but patients receiving SO-OO showed decreases in γ-GT and total bilirubin; other liver function markers were not different. Two studies did not observe any differences in liver function markers between the IVLEs that they compared [11,15].

3.5 Effect of IVLEs on markers of inflammation

No effects on markers of inflammation have been reported after using different IVLEs [11,12,15] (Table 4).

3.6 Effect of IVLEs on antioxidant status and oxidative stress

One study [12] reported that SMOF resulted in increased serum levels of the antioxidant α-tocopherol, but this was not seen in another study which used SO-MCT-FO [15]. Rubin et al. [10] observed no difference in blood levels of fatty acid peroxidation markers between patients receiving SO and structured SO-MCT.

3.7 Effect of IVLEs on adverse events

Four studies reported no differences in adverse events between patients receiving different IVLEs [10,11,15,16] (Table 4). Klek et al. [12] found that serious adverse events were more common among patients receiving SO than those receiving SMOF. In that study 51 adverse events occurred in 21 patients in the SO group while 31 adverse events occurred in 15 patients in the SMOF group ($p = 0.11$). With regard to serious adverse events, two were recorded in two patients in the SMOF group, while 8 patients in the SO group experienced a total of 10 serious adverse events ($p = 0.03$).

4. Discussion

This systematic review included three studies not included in a systematic review on this topic that was published in 2018 with a literature search conducted in November 2015 [9]. Two of these studies [15,16] were published since the previous literature search was conducted, while the third [17] was an older study, not previously included, perhaps because it only reports on erythrocyte fatty acids. In total six studies were included in the current review. These compared SO with structured SO-MCT [10], with SO-OO [11], with SMOF [12], with SO-MCT [17] and with SO-MCT, SO-OO and SMOF [16]; the other study compared SO-MCT with SO-MCT-FO [15]. Despite the greater number of included studies and the greater range of comparisons made, the overall conclusion of this systematic review is little different from that of the previous one: there are modest differences amongst the various IVLEs in adults receiving HPN, those containing olive oil or fish oil may be superior to pure SO, there are too few studies to make a definitive conclusion on superiority of one formulation over another, and more, larger studies that investigate multiple relevant outcomes are needed. LEs containing olive oil or fish oil may have an advantage over pure SO with regard to liver function [10,16] and antioxidant status [10]. No differences in inflammatory biomarkers have been reported [11,12,15]. Adverse events in this patient group are little different according to the LE used, although serious adverse events may be fewer with SMOF [12]. Thus, the conclusion of benefit from including OO or FO is supported by fairly weak evidence, calling for larger studies comparing multiple LEs in this group of patients. Longer term effects of changes in fatty acid availability in blood and cells need to be evaluated as these changes might be expected to reduce inflammation, improve metabolism and protect the liver.

Studies included in this review were generally of short duration; five lasted one to three months [10,11,12,15,17] while one was of 12 months duration [16]. Intravenous supply of fatty acids provides them more quickly to cells and tissues than oral/enteral supply. With oral provision of EPA and DHA

different cells acquire those fatty acids over the course of weeks to months and erythrocytes are considered to require 4 to 6 months to reach saturation with EPA and DHA [18]. With intravenous administration, the rate of acquisition of EPA and DHA into erythrocytes and white blood cells is relatively rapid [19,20], and may be faster than seen with the oral route. Nevertheless, the acquisition of bioactive fatty acids is related to the rate of turnover of the pool (e.g. erythrocytes, liver) and therefore it is likely that several months will be required for cell and tissue pools to reach maximum accumulation of bioactive fatty acids. Because the functional effects of fatty acids often require their incorporation into cells [8], a study duration of several months or longer could be required to see effects on biomarkers and on clinical outcomes. Therefore, some of the studies performed to date could be too short to result in meaningful physiological changes and improved patient outcomes. The longest study conducted to date [16], identified a decrease in some markers of liver (dys)function after 12 months of SO-OO. No effects of SMOF on these markers was seen [16], meaning that an earlier report of lower markers after four weeks of SMOF [12] was not confirmed. The reasons for this are unclear. A recent study comparing the effects of SO-OO and SMOF in adult HPN patients over two months, but not as a randomised controlled trial, reported that SO-OO resulted in a decrease in ALT and that SMOF was without effect on liver function markers [21]. This finding is generally consistent with that of Klek et al. [16].

SO is abundant in the EFAs linoleic and α-linolenic. There is a concern that lowering the amount of SO used in an IVLE would decrease delivery of EFAs to the extent that EFA deficiency might occur. Four studies included in this systematic review reported on fatty acids in one or more blood pools [11,12,15,17]. Infusion of an IVLE containing OO increases oleic acid and infusion of a FO-containing IVLE increases EPA and DHA. These increases can be associated with lowering the amount of linoleic acid present, probably due to competition between different fatty acids for incorporation into lipid pools and cell membranes, although there could be effects on the pathway of polyunsaturated fatty acid metabolism and its sensitivity to hormones, as suggested elsewhere [22]. The markers of EFA deficiency are increased mead acid and an increase in the ratio of mead to arachidonic acid. The one study that reported on this [11], found that SO-OO increased mead acid but the ratio of mead to arachidonic acid remained below the threshold of 0.2 that indicates EFA deficiency. This would indicate that use of SO-OO is unlikely to result in EFA deficiency, a conclusion supported by other studies with SO-OO in adults receiving HPN [23,24]. Nevertheless, mead acid should be monitored in a long-term study of SO-OO in this patient group. Mead acid was not reported in the study of Klek et al. with SMOF [12] or in the study of Bohnert et al. with SO-MCT-FO [15]. However, Osowska et al. [21] reported on mead acid and its ratio with arachidonic acid in plasma and in plasma phospholipids before and after two months of SO-OO or SMOF in adult HPN patients: there was no change in the group receiving SMOF while in the group receiving SO-OO the ratio actually decreased significantly. These observations suggest little concern about EFA deficiency in adult HPN

patients receiving either SO-OO or SMOF. This lack of concern should not be extrapolated to infants and children receiving HPN, and the appropriate studies need to be carried out in those populations.

Although publication bias was minimised as much as possible through inclusion/exclusion criteria, there are some points that should be raised. The omission of articles that were not written in English may have decreased the final pool of articles that were included. Also, some completed studies may not have yet been available on the electronic databases that were searched. Additional searchers were performed on Google Scholar and other databases, but these did not yield any studies that were not already identified.

5. Conclusion

LEs containing olive oil or fish oil may be superior to pure SO with regard to the long-term effects of increased α-tocopherol and an altered blood and cell fatty acid profile. Based on data from trials conducted to date, there are modest differences in clinically relevant outcomes (liver function, adverse events) reported between different IVLEs in adults receiving HPN. However, there are too few studies to make a definitive conclusion on superiority of one formulation over another and more, larger studies that investigate multiple relevant outcomes (liver function, inflammation, oxidative stress, EFA deficiency) are needed.

Conflicts of Interest

PCC has received fees for advising and speaking honoraria from Fresenius-Kabi, B. Braun Melsungen, and Baxter Healthcare. SA and JKI have no conflicts to declare.

References

1. Wanten G, Calder PC, Forbes A. Managing adult patients who need home parenteral nutrition. BMJ 2011;342:696-701.
2. Pironi L, Arends J, Baxter J, Bozzetti F, Pelaez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr 2015;34:171-180.
3. Pironi L, Goulet O, Buchman A, Messing B, Gabe S, Candusso M, et al. Home Artificial Nutrition and Chronic Intestinal Failure Working Group of ESPEN. Outcome on home parenteral nutrition for benign intestinal failure: A review of the literature and benchmarking with the European prospective survey of ESPEN. Clin Nutr 2012;31:831-845.
4. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr 2016;35:247-307.
5. Holman RT. Essential fatty acid deficiency. Progr Lipid Res 1968;9:275-348.
6. Calder PC. Lipids for intravenous nutrition in hospitalised adult patients: a multiple choice of options. Proc Nutr Soc 2013;72:263-276.
7. Beath SV, Kelly DA. Total parenteral nutrition-induced cholestasis: prevention and management. Clin Liver Dis 2016;20:159-176.
8. Calder PC. Functional roles of fatty acids and their effects on human health. JPEN J Parent and Enteral Nutr 2015 39 (1 Suppl):18S-32S.
9. Jones CJ, Calder PC. 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. Clin Nutr 2018;37:285-291.

10. Rubin M, Moser A, Vaserberg N, Greig F, Levy Y, Spivak H, et al. Structured triacylglycerol emulsion, containing both medium- and long-chain fatty acids, in long-term home parenteral nutrition: A double-blind randomized cross-over study. Nutrition 2000;16: 95-100.
11. Vahedi K, Atlan P, Joly F, Le Brun A, Evard D, Perennec V, et al. A 3-month double-blind randomised study comparing an olive oil- with a soyabean oil-based intravenous lipid emulsion in home parenteral nutrition patients. Brit J Nutr 2005;94:909-916.
12. Klek S, Chambrier C, Singer P, Rubin M, Bowling T, Staun M, et al. Four-week parenteral nutrition using a third generation lipid emulsion (SMOFlipid)--a double-blind, randomised, multicentre study in adults. Clin Nutr 2013; 32:224-231.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement PLoS Med 2009;6:e1000097.
14. Higgins JPT, Green S (Eds.), Cochrane handbook for systematic reviews of interventions, The Cochrane Collaboration 2011; available from: www.cochrane-handbook.org.
15. Bohnert H, Maurer M, Calder PC, Pratschke J, Thul P, Muller V. Efficacy of a long-term home parenteral nutrition regimen containing fish oil-derived n-3 polyunsaturated fatty acids: a single-centre, randomized, double blind study. Nutr J 2018;17:113
16. Klek S, Szczepanek K, Scislo L, Walewska E, Pietka M, Pisarska M, Pedziwiatr M. Intravenous lipid emulsions and liver function in adult chronic intestinal failure patients: results from a randomized clinical trial. Nutrition 2018;55-56:45-50.
17. Dahlan W, Richelle M, Kulapongse S, Rössle C, Deckelbaum RJ, Carpentier YA. Effects of essential fatty acid contents of lipid emulsions on erythrocyte polyunsaturated fatty acid composition in patients on long term parenteral nutrition Clin Nutr 1992;11:262-268.
18. Browning LM, Walker CG, Mander AP, West AL, Madden J, Gambell JM et al. Incorporation of eicosapentaenoic and docosahexaenoic acids into lipid pools when given as supplements providing doses equivalent to typical intakes of oily fish. Am J Clin Nutr 2012;96:748-758.
19. Barros KV, Cassulino AP, Schalch L, Della Valle Munhoz E, Manetta JA, Noakes PS, Miles EA, Calder PC, Flor Silveira VL. Supplemental intravenous n-3 fatty acids and n-3 fatty acid status and outcome in critically ill elderly patients in the ICU receiving enteral nutrition. Clin Nutr 2013;32:599-605.
20. Al-Taan O, Stephenson JA, Spencer L, Pollard C, West AL, Calder PC, Metcalfe M, Dennison AR. Changes in plasma and erythrocyte omega-6 and omega-3 fatty acids in response to intravenous supply of omega-3 fatty acids in patients with hepatic colorectal metastases. Lipids Health Dis 2013;12:64.
21. Osowska S, Kunecki M, Sobocki J, Tokarczyk J, Majewska K, Omidi M, Radkowski M, Fisk HL, Calder PC. Effect of changing the lipid component of home parenteral nutrition in adults. Clin Nutr 2019;38:1355-1361.
22. Pironi L, Guidetti M, Verrastro O, Iacona C, Agostini F, Pazzeschi C, Sasdelli AS, Melchiorre M, Ferreri C. Functioanl lipidomics in patients on homne parenteral nutrition: effects of lipid emulsions. World J Gastroenterol 2017;23:4604-1414.
23. Reimund JM, Rahmi G, Escalin G, Pinna G, Finck G, Muller CD, et al. Efficacy and safety of an olive oil-based intravenous fat emulsion in adult patients on home parenteral nutrition. Alimet Pharmacol Therapeut 2005;21:445-454.
24. Olthof ED, Roelofs HM, Fisk HL, Calder PC, Wanten GJ. No clinical or biochemical evidence for essential fatty acid deficiency in home patients who depend on long-term mixed olive oil- and soybean oil-based parenteral nutrition. JPEN J Parent Enteral Nutr 2016;40:982-988.

362 **Table 1**

363 Comparison of the compositions of commercially available IVLEs

Lipid emulsion	Soybean oil (SO)	SO-MCT	Structured SO-MCT	SO-OO	SO-MCT-OO-FO	SO-MCT-FO
Trade name	Intralipid	Lipofundin	Structolipid	ClinOleic	SMOFlipid	Lipidem or Lipoplus
Lipid source (% by weight)	SO (100)	SO (50) MCT (50)	SO (64) MCT (36)	SO (20) OO (80)	SO (30) MCT (30) OO (25) FO (15)	SO (40) MCT (50) FO (10)
Linoleic acid (% of total FAs)	53	27	35	19	23	27
Alpha-linolenic acid (% of total FAs)	8	4	5	2.3	2	4
EPA + DHA (% of total FAs)	0	0	0	0.5	5	6
Oleic acid (% of total FAs)	24	11	14	62	33	14
Ratio of n-6 to n-3 PUFAs	~7	~7	~7	~7	~3.3	~2.7

364 DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FO, fish oil; MCT, medium chain
365 triglycerides; OO, olive oil; SO, soybean oil

366 **Table 2.** Characteristics of the included studies

Reference	IVLEs used	Sample size (randomised /completed)	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 [10]	Structured 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 Structured SO-MCT	12/11	7/5	45.3	60	2 (1 per IVLE)	SBS (n=4) Crohn's (n=8)
Vahedi et al. 2005 [11]	SO-OO	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 [12]	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)
Bohnert et al. 2018 [15]	SO-MCT-FO	21/15	14/7	55.8	NR	2	Malabsorption (n=21)
	SO-MCT	21/18	12/9	58.0	NR	2	Malabsorption (n=21)
Klek et al. 2018 [16]	SO-MCT	22/18	8/10	56.3	23 days	12	Vascular (n=7) Crohn's (n=3) Surgical (n=2) Radiation enteritis (n=2) GI fistula (n=1) Malabsorption (n=1) Motility disorders (n=1) Benign GI obstruction (n=1)
	SO-OO	22/17	7/10	54.8	22 days	12	Vascular (n=8) Crohn's (n=3) Surgical (n=2) Radiation enteritis (n=1) Malabsorption (n=1) Trauma (n=1) Other (n=1)
	SMOF	22/16	8/8	47.8	25 days	12	Vascular (n=7) Crohn's (n=4) Surgical (n=2) GI fistula (n=1) Trauma (n=1) Necrotising enterocolitis (n=1)
	SO	22/14	5/9	59.6	25 days	12	Vascular (n=6) Crohn's (n=2) Surgical (n=2) Radiation enteritis (n=1) GI fistula (n=1) Motility disorder (n=1) Other (n=1)
Dahlan et al. 1992 [17]	SO then SO-MCT or SO-MCT then SO	5/5	2/3	29	NR	3 months per IVLE	Inflammatory bowel disease (n=5)

FO, fish oil; GI, gastrointestinal; IVLE, intravenous lipid emulsion; MCT, medium chain triglycerides; NR, Not reported; OO, olive oil; SBS, short bowel syndrome; SMOF, soybean oil-medium chain triglycerides-olive oil-fish oil; SO, soybean oil.

Table 3. Bias table based on “Cochrane Tool for Assessing Bias”

Reference	Rubin et al. 2000 [10]	Vahedi et al. 2005 [11]	Klek et al. 2013 [12]	Bonhert el al. 2018 [15]	Klek et al. 2018 [16]	Dahlan et al. (1992) [17]
Random sequence generation (selection bias)					Method of randomisation not specified	Method of randomisation not specified
Allocation concealment (selection bias)						No mention of if or how the allocation was concealed
Blinding of participants and personnel (performance bias)						Does not mention if patients were blinded
Blinding of outcome assessment (detection bias)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Incomplete outcome data (attrition bias)		Insufficient reporting of attrition: no reason given for reduced sample size in some results tables	Insufficient reporting of attrition: no reason given for reduced sample size in some results tables	Insufficient reporting of attrition: no reason given for reduced sample size in some results tables	Insufficient reporting of attrition: reasons given for only 16 out of out of 23 patients who were lost to follow up	
Selective reporting (reporting bias)		Data not reported for some outcomes for some patients	Data not reported for some outcomes for some patients	Data not reported for some outcomes for some patients		

Table 4. Summary of results from the six included studies

Reference	Study detail	IVLE used	Liver function test	Inflammation and peroxidation status	Clinical outcomes
Rubin et al. 2000 [10]	RCT, adults, n = 22, 4 weeks	SO vs structured SO-MCT	ALP, ALT, AST and γ-GT abnormal in 2 patients when receiving SO; otherwise no differences in ALP, ALT, AST, γ-GT and bilirubin	Similar lipid peroxidation	Similar clinical safety and AEs (vomiting n = 4 for SO, n = 5 for SO-MCT)
Vahedi et al. 2005 [11]	RCT, adults, n = 13, 3 months	SO vs SO-OO	No differences in liver abnormalities	No change or difference in CRP	Similar AEs
Klek et al. 2013 [12]	RCT, adults, n = 75, 4 weeks	SO vs SMOF	Normal ALP, ALT, AST, γ-GT and bilirubin, but ALT, AST and 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 receptor II or CRP	Serious AEs more frequent with SO (p = 0.03)
Bohnert el al. (2018) [15]	RCT, adults, n = 42, 2 months	SO-MCT vs SO-MCT-FO	No differences in ALP, ALT, AST, γ-GT and bilirubin	No statistically significant difference in α-tocopherol, TNF, IL-6, IL-10 or CRP	No AE related to treatment was identified
Klek et al. (2018) [16]	RCT, adults, n = 88, 12 months	SO vs SO-MCT vs SO-OO vs SMOF	No statistically significant differences in liver function parameters (GPT, GOT, ALP, γ-GT, bilirubin), apart from a decrease in total bilirubin and γ-GT after 12 months with SO-OO (p = 0.0023 and 0.0079)	NR	No serious AEs recorded
Dahlan et al. (1992) [17]	RCT, adults, n = 5, 3 months	SO vs SO-MCT	NR	NR	NR

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; FO, fish oil; IL, interleukin; IVLE, intravenous lipid emulsion; γ-GT, gamma-glutamyltransferase; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; MCT, medium chain triglycerides; NR, Not reported; OO, olive oil; RCT, randomized controlled trial; SMOF, soybean oil-medium chain triglycerides-olive oil-fish oil; SO, soybean oil; TNF, tumour necrosis factor.

Figure 1. PRISMA flow diagram showing multistage search strategy and study selection