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SYSTEMATIC REVIEW

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Alternative lipid emulsions in the critically ill: a systematic review of the evidence

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Abstract *Purpose:* Parenteral lipid emulsions (LEs) are commonly rich in long-chain triglycerides derived from soybean oil (SO). SO-containing emulsions may promote systemic inflammation and therefore may adversely affect clinical outcomes. We hypothesized that alternative oil-based LEs (SO-sparing strategies) may improve clinical outcomes in critically ill adult patients compared to products containing SO emulsion only. The purpose of this systematic review was to evaluate the effect of parenteral SO-sparing strategies on clinical outcomes in intensive care unit (ICU) patients. *Methods:* We searched computerized databases from 1980 to 2013. We included randomized controlled trials (RCTs) conducted in critically ill adult patients that evaluated SO-sparing strategies versus SO-based LEs in the context of parenteral nutrition. *Results:* A total of 12 RCTs met the inclusion criteria. When the results of these RCTs were statistically aggregated, SO-sparing strategies were associated with clinically important reductions in mortality (risk ratio, RR 0.83; 95 % confidence intervals, CI 0.62, 1.11; $P = 0.20$), in duration of ventilation (weighted mean difference, WMD −2.57; 95 % CI −5.51, 0.37; $P = 0.09$), and in ICU length of stay (LOS) (WMD −2.31; 95 % CI −5.28, 0.66; $P = 0.13$) but none of these differences were statistically significant. SO-sparing strategies had no effect on infectious complications (RR 1.13; 95 % CI 0.87, 1.46; $P = 0.35$). *Conclusion:* Alternative oil-based LEs may be associated with clinically important reductions in mortality, duration of ventilation, and ICU LOS but lack of statistical precision precludes any clinical recommendations at this time. Further research is warranted to confirm these potential positive treatment effects.

Keywords Alternative lipid emulsions · Soybean oil reducing strategies · Critically ill

Introduction

Lipid emulsions (LEs) are an essential constituent of parenteral nutrition (PN) [1] and are considered an important source of energy, essential fatty acids (FA), and vitamins E and K [2–4]. However, the current literature suggests that soybean oil (SO) and safflower-based LEs which are rich in the ω-6 fatty acid linoleic acid might promote production of pro-inflammatory prostanoids and leukotrienes resulting in increased oxidative stress and systemic inflammation [5, 6] and may be associated with worse clinical outcomes [7].

Over the past three decades, different generations of alternative oil-based LEs have been developed, which could have less pro-inflammatory effects, less immune suppression, and more antioxidant effects than the standard SO-based LEs [8–10]. These SO-sparing strategies consist of different formulations of SO combined with medium-chain triglycerides (MCTs), olive oil (OO) which contains the ω-9 monounsaturated FA (MUFA) oleic acid, and fish oil (FO) which contains ω-3 FA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The purpose of the current study was to provide an up-to-date systematic review and meta-analysis of all randomized clinical trials (RCTs) of alternative oil-based LEs, compared to SO emulsion products, evaluating clinically relevant outcomes in the critically ill. Preliminary results of this systematic review were previously published in abstract form [11].

Methods

Study identification

We conducted a systematic review of the published literature to identify all relevant clinical trials using text word or MeSH headings containing the following: ω-6 sparing, ω-6 reducing, alternative fat emulsions, fish oil lipid emulsions, ω-3, ω-9, olive oil lipid emulsions, MCT lipid emulsions, randomized, blind, clinical trial, nutritional support, parenteral nutrition, lipid emulsions, critical illness, and critically ill. Our comprehensive search strategy included non-English articles.

We included studies if they met all the following eligibility criteria:

1. Study design: randomized controlled trials (RCTs).
2. Population: critically ill adult patients (>18 years old).
3. Intervention: parenteral strategies to reduce the overall load of ω-6 FA (alternative ω-6-sparing LEs) versus ω-6 oil-based LEs (LCT in the control group).
4. Study outcomes: mortality was the primary outcome for this meta-analysis. Secondary outcomes were intensive care unit (ICU) and hospital length of stay (LOS), infections, and mechanical ventilation (MV) days. We excluded the clinical studies that reported only biochemical, metabolic, immunologic, or nutritional outcomes. Critically ill patients were defined as patients admitted to an ICU who had an urgent or life-threatening complication (high baseline mortality rate ≥5 %) to distinguish them from patients with elective surgery who are also cared for in some ICUs but have a low baseline mortality rate (<5 %).

Data extraction and risk of bias assessment

Two reviewers independently extracted data using a data abstraction form with a scoring system [7]. We scored the methodological quality of individual trials considering the following key features of high-quality studies: (a) extent to which randomization was concealed, (b) blinding, (c) analysis was based on the intention-to-treat (ITT) principle, (d) comparability of groups at baseline, (e) extent of follow-up, (f) description of treatment protocol and co-interventions, and (g) definition of clinical outcomes. Each individual study was scored from 0 to 14. Disagreement was resolved by consensus between both reviewers. We attempted to contact the authors of included trials and requested missing or unclear information. We designated a study as level 1 if all of the following criteria were fulfilled: concealed randomization, blinded outcome adjudication, and an ITT analysis. A study was considered a level 2 study if any one of the above characteristics was unfulfilled.

Data synthesis

The primary outcome of the systematic review was overall mortality. From all trials, we combined hospital mortality where reported. If hospital mortality was not reported, we used ICU mortality or 28-day mortality. Secondary outcomes included infections, MV days, and ICU LOS. We used definitions of infections as defined by the authors in their original papers. We analyzed data using RevMan 5.1 with a random effects model. We calculated pooled relative risks using the Mantel–Haenszel estimator for dichotomous outcomes and weighted mean differences (WMDs) were estimated by the inverse variance approach for continuous outcomes, with associated 95 % CIs. The random effects model of DerSimonian and Laird was used to estimate variances for the Mantel–Haenszel and inverse variance estimators [12]. The possibility of publication bias was assessed by generating funnel plots and testing asymmetry of outcomes using methods proposed by Rucker et al. [13]. Statistical heterogeneity was assessed by the I^2 statistic [14]. We considered $P < 0.05$ to be statistically significant and $P < 0.20$ as an indicator of trend.

Table 1 Randomized clinical trials evaluating type of lipids (parenteral nutrition) in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)[a]		Infections # (%)[b]	
Long-chain triglyceride (LCT) plus medium-chain triglycerides (MCT) vs. LCT							
Nijveldt et al. [53]	ICU, septic surgical patients, trauma ($N = 20$)	C. Random: not sure ITT: yes Blinding: double (10)	PN + Lipofundin (50 % LCT + 50 % MCT) vs. PN + intralipid (100 % LCT, soybean)	LCT + MCT ICU, 2/12 (17)	LCT ICU, 1/8 (13)	LCT + MCT NR	LCT NR
Lindgren et al. [54]	ICU patients, sepsis, multi-trauma ($N = 30$)	C. Random: yes ITT: yes Blinding: yes (12)	PN + Structolipid (64 % LCT + 36 % MCT) vs. PN + intralipid (100 % LCT, soybean)	LCT + MCT 1/15 (7)	LCT 0/15 (0)	LCT + MCT 6/15 (40)	LCT 4/15 (27)
Garnacho-Montero et al. [55]	Surgical ICU Patients with peritonitis and abdominal sepsis ($N = 72$)	C. Random: not sure ITT: no Blinding: no (6)	PN + Lipofundin (50 % LCT + 50 % MCT) vs. PN with intralipid (100 % LCT, soybean) Both groups received PN with 45 % branched chain amino acids	LCT + MCT ICU, 8/35 (23) Hospital, 11/35 (31)	LCT ICU, 11/37 (30) Hospital, 13/37 (35)	LCT + MCT NR	LCT NR
Iovinelli et al. [56]	Patients with COPD requiring ventilation ($N = 24$)	C. Random: yes ITT: yes Blinding: no (7)	PN + Lipofundin (50 % LCT + 50 % MCT) vs. 100 % LCT (100 % LCT, soybean). Both groups received 50 % of non-protein calories as lipids	LCT + MCT ICU, 2/12 (17)	LCT ICU, 3/12 (25)	LCT + MCT Catheter-related 1/12 (8)	LCT Catheter-related 2/12 (17)
Fish oil (ω-3)-containing emulsions in PN-fed patients vs. LCT or LCT + MCT							
Grecu et al. [60]	Patients with abdominal sepsis ($N = 54$) (15/54 in ICU)	C. Random: yes ITT: yes Blinding: double (12)	PN + Omegaven (10 % fish oils) plus LCTs vs. PN with LCT	Omegaven + LCT ICU, 2/28 (7)	LCT ICU, 3/26 (12)	Omegaven VAP, 0/8[c]	LCT VAP, 1/7[c] (14)
Friesecke et al. [61]	Medical ICU patients ($N = 166$)	C. Random: yes ITT: yes Blinding: double (10)	PN + Lipofundin MCT (50 % LCT + 50 % MCT) + Omegaven (10 % fish oil) vs. Lipofundin MCT (50 % LCT + 50 % MCT)	LCT + MCT + FO 28 day, 18/83 (22)	LCT + MCT 28 day, 22/82 (27)	LCT + MCT + FO 10/83 (12)	LCT + MCT 11/82 (13)
Wang et al. [62]	Severe acute pancreatitis patients in ICU ($N = 56$)	C. Random: no ITT: yes Blinding: double (11)	PN + Omegaven (10 % fish oils) plus Lipovenos (LCTs, soybean oil) (ω-3/ω-6 ratio was 1:4) vs. PN with Lipovenos (LCTs, soybean oil). Both received same amounts of lipids (1 g/kg/day)	Omegaven ICU, 0/28 (0)	LCT ICU, 2/28 (7)	Omegaven 6/28 (21)	LCT 9/28 (32)
Barbosa et al. [63]	ICU patients with SIRS or sepsis requiring PN ($N = 25$)	C. Random: yes ITT: yes Blinding: single (10)	PN + Lipoplus (50 % MCT, 40 % LCTs soybean oil, 10 % FOl) vs. Nutriflex LipidSpecial (50 % MCT, 50 % LCT, soybean oil). Both received same amounts of lipids (~1 g/kg/day)	MCT + LCT + FO 5 day, 2/13 (15) 28 day, 4/13 (31)	MCT + LCT 5 day, 1/10 (10) 28 day, 4/10 (40)	MCT + LCT + FO NR	MCT + LCT NR
Olive oil-containing emulsions vs. LCT or LCT + MCT							
Garcia-de-Lorenzo et al. [57]	Severe burn patients, burn severity index ≥7, TBSA >30 % ($N = 22$)	C. Random: not sure ITT: yes Blinding: double (10)	PN with Clinoleic 20 % (80 % olive oil, 20 % soybean oil, (63 % ω-9, 37 % ω-6 = restricted linoleic acid {ω-6} content) vs. Lipofundin (50 % LCT + 50 % MCT)	Clinoleic ICU, 4/11 (36)	Lipofundin ICU, 4/11 (36)	Clinoleic 6/11 (55)	Lipofundin 6/11 (55)
Huschak et al. [58][d]	ICU trauma patients ($N = 33$)	C. Random: yes ITT: yes Blinding: none (7)	PN high fat (lipid/glucose 75:25) + Clinoleic (80 % olive oil, 20 % soybean oil) + EN Glucerrna (lipid/glucose 60:40) vs. PN high carbohydrate (lipid: glucose 37:63) + Lipofundin (50 % LCT + 50 % MCT) + EN Fresubin HP Energy (lipid/glucose 44:56)	High fat + Clinoleic ICU, 4/18 (22)	Low fat + LCT + MCT ICU, 1/15 (7)	High fat + Clinoleic Low fat + LCT + MCT NR	

Table 1 continued

Study	Population	Methods (score)	Intervention	Mortality # (%)[a]		Infections # (%)[b]	
Umpierrez et al. [59]	Medical surgical ICU pts post op (88 % emergency surgeries) ($N = 100$)	C. Random: yes ITT: yes Blinding: double (14)	PN with Clinoleic 20 % (80 % olive oil, 20 % soybean oil, ω-6/ω-3 = 9:1) vs. intralipid (100 % soybean oil, ω-6/ω-3 = 7:1)	Clinoleic Hospital, 5/51 (10)	Intralipid Hospital, 8/49 (16)	Clinoleic 29/51 (57) Pneumonia 7/51 (14)	Intralipid 21/49 (43) 5/49 (10)
Pontes-Arruda et al. [64]	ICU pts requiring PN from 8 ICUs and 3 countries ($N = 204$)	C. Random: yes ITT: yes Blinding: no (9)	PN with Clinoleic ($N = 103$) vs PN with a MCT/LCT-based IVLE ($N = 101$)	Clinoleic ICU, 19/103 (24) 28-day, 24/103 (27)	MCT/LCT ICU, 21/101 (21) 28-day, 26/101 (26)	Clinoleic All infections 39/103 (38) ICU-acquired infections 28/103 (27) VAP/lower respiratory infections 9/103 (9)	MCT/LCT 35/101 (35) 23/101 (23) 11/101 (11)

Critically ill patients were defined as patients admitted to an ICU who had an urgent or life-threatening complication (high baseline mortality rate ≥5 %) to distinguish them from patients with elective surgery who are also cared for in some ICUs but have a low baseline mortality rate (<5 %)

ARDS acute respiratory distress syndrome, *C.Random* concealed randomization, *DHA* docosahexaenoic acid, *EN* enteral nutrition, *EPA* eicosapentaenoic acid, *FO* fish oil, *ICU* intensive care unit, *ITT* intention to treat, *IV* intravenous, *LCT* long-chain triglycerides, *MCT* medium-chain triglycerides, *N* number of patients, *NR* not reported, *PN* parenteral nutrition, *SIRS* systemic inflammatory response syndrome, *VAP* ventilator-associated pneumonia, *ω-3* omega 3, *ω-6* omega 6, *ω-9* omega 9

[a] Hospital mortality unless specified

[b] Number of patients with infections unless specified

[c] Data obtained from author, 8 out of 28 in Omegaven and 7 out of 26 in LCT group were in ICU

[d] Intervention includes high fat low carbohydrates PN plus fish oil

Hypotheses testing

Given the different ω-6 FA-sparing strategies and the heterogeneity of trial design, we performed pre-specified, hypothesis-generating subgroup analyses to attempt to elucidate potentially more beneficial treatment strategies. We compared the results of trials that provided (a) long-chain triglycerides (LCTs) plus MCT to an LCT emulsion; (b) ω-3 oil-based LEs to an LCT or LCT/MCT mixture, and (c) ω-9 oil-based LEs to an LCT or LCT + MCT mixture.

Post hoc, we determined that the control group solutions included both LCT and an LCT + MCT mixture. To evaluate the influence of this heterogeneity, we conducted a sensitivity analysis removing the RCTs that utilized an LCT plus an MCT-based strategy in the control group.

Results

Study identification and selection

A total of 51 potentially eligible RCTs were identified. Of these, we excluded 39 trials due to the following reasons: 22 trials [15–36] trials did not include ICU patients (mostly elective surgery and cancer patients), 11 trials [31, 37–46] did not evaluate clinically important outcomes; 2 trials [47, 48] did not include SO-based LE in the control group; 1 trial [49] compared LCT versus another LCT emulsion without reduction in SO; 1 trial [50] was conducted in a pediatric population; 1 trial [51] had a short duration of intervention (12 h of lipid emulsion infusion during the first day); 1 trial included patients with poisoning and not representative of ICU patients [52]. In the end, 12 RCTs [53–64] enrolling a total of 806 patients met the inclusion criteria and were included in this systematic review (see Tables 1, 2). The authors reached 100 % agreement for inclusion of relevant trials in this review. The mean methodological score of all trials was 9.8 (6–14). Randomization was concealed in 8/12 (67 %) trials, ITT analysis was performed in 11/12 (92 %) trials, and 8/12 (67 %) trials were double blinded. There were five level 1 studies and seven level 2 studies. The details of the methodological quality of the individual trials are shown in Table 1.

Meta-analysis of primary outcome

When the results of the 12 RCTs [53–64] that evaluated mortality were statistically aggregated, ω-6-sparing strategies were associated with a reduction in mortality that was not statistically significant [risk ratio (RR) 0.83; 95 % confidence intervals (CI) 0.62, 1.11; $P = 0.20$, heterogeneity $I^2 = 0$ % see Fig. 1]. In addition, when a

Table 2 Outcomes of included trials on ω-6-reducing strategies using lipid emulsions

Study	LOS days		Ventilator days		Other	
Long-chain triglyceride (LCT) plus medium-chain triglycerides (MCT) vs. LCT						
Nijveldt et al. [53]	LCT + MCT	LCT	LCT + MCT	LCT	NR	
	13.8 ± 2.9 (12)	17.4 ± 3.0 (8)	NR	NR		
Lindgren et al. [54]	LCT + MCT	LCT	LCT + MCT	LCT	LCT + MCT	LCT
	NR	NR	NR	NR	Adverse effects	
					5/15 (33)	4/15 (27)
					Nitrogen balance at day 3	
					2.6 ± 5.6 g	−11.7 ± 4.8 g
Garnacho-Montero et al. [55]	LCT + MCT	LCT	LCT + MCT	LCT	LCT + MCT	LCT
	ICU, 16.6 ± 6.1 (35)	ICU, 15.8 ± 7 (37)	NR	NR	Retinol binding protein	
					1.7 ± 1	0.8 ± 0.6
					Nitrogen balance	
					14.2 ± 2.9	11.6 ± 4
Iovinelli et al. [56]	LCT + MCT	LCT	LCT + MCT	LCT	LCT + MCT	LCT
	NR	NR	10.6 ± 3.0 (12)	13.4 ± 3.5 (12)	Time before weaning	
					52 ± 36 h	127 ± 73 h
Fish oil (ω-3)-containing emulsions in PN-fed patients vs. LCT or LCT + MCT						
Grecu et al. [60]	Omegaven	LCT	Omegaven	LCT	Omegaven	LCT
	ICU, 3.32 ± 1.48 (8)	ICU, 9.28 ± 3.08 (7)	2.83 ± 1.62 (8)	5.23 ± 2.80 (7)	Patients undergoing reoperation for septic episode	
	Hospital, 11.68 ± 2.04 (28)	Hospital, 20.46 ± 3.27 (26)				
					2/28 (7)	8/26 (31)
Friesecke et al. [61]	FO	LCT	LCT + MCT + FO	LCT + MCT	LCT + MCT + FO	LCT + MCT
	ICU, 28 ± 25 (83)	ICU, 23 ± 20 (82)	22.8 ± 22.9 (83)	20.5 ± 19.0 (82)	Urinary tract infections	
					6/83 (7)	4/82 (5)
					Catheter-related infections	
					1/83 (1)	3/83 (4)
					Total EN energy intake (kcal/kg)	
					22.2 ± 5.5	21.6 ± 5.6
Wang et al. [62]	NR	NR	NR	NR	Omegaven	LCT
					Surgery of infected pancreatic necrosis	
					3/28 (11)	6/28 (21)
Barbosa et al. [63]	MCT + LCT + FO	MCT + LCT	MCT + LCT + FO	MCT + LCT	MCT + LCT + FO	MCT + LCT
	ICU, 12 ± 14.4[a] (13)	ICU, 13 ± 12.6[a] (10)	10 ± 14.4 (13)	11 ± 12.64 (10)	2,057 ± 418 kcal	1,857 ± 255 kcal
	Hospital, 22 ± 25.2[a] (13)	Hospital, 55 ± 50.6[a] (10)				
Olive oil-containing emulsions vs. LCT or LCT + MCT						
Garcia-de-Lorenzo et al. [57]	Clinoleic	Lipofundin	Clinoleic	Lipofundin	Clinoleic	Lipofundin
	ICU, 32.9 ± 10.6[a] (11)	ICU, 41.8 ± 16.3[a] (11)	11.0 ± 11.93[a] (11)	13.0 ± 16.25[a] (11)	Multiple organ dysfunction score	
	Hospital, 57 ± 15.3[a] (11)	Hospital, 64.9 ± 27.2[a] (11)				
					11.0 ± 3.6	13.0 ± 4.9

Table 2 continued

Study	LOS days		Ventilator days		Other	
Huschak et al. [58]	High fat + Clinoleic ICU, 17.9 ± 11.2 (18)	Low fat + LCT + MCT ICU, 25.1 ± 7.0 (15)	High fat + Clinoleic 13.0 ± 8.9 (18)	Low fat + LCT + MCT 20.4 ± 7.0 (15)	High fat + Clinoleic Total energy intake (kcal/kg) 17.9 ± 6.3	Low fat + LCT + MCT 22.3 ± 4.2
Umpierrez et al. [59]	Clinoleic ICU, 17 ± 18 (51) Hospital, 40.8 ± 36 (51)	Intralipid ICU, 15.2 ± 14 (49) Hospital, 46.7 ± 48 (51)	Clinoleic NR	Intralipid NR	Clinoleic Total energy intake (kcal/kg) 22 ± 6	Intralipid 22 ± 5
Pontes-Arruda et al. [64]	Clinoleic ICU, 12 (7–17) Hospital, 21 (15–25)	MCT/LCT ICU, 11 (5–14) Hospital, 18 (13–23)	NR	NR	Clinoleic Nutritional Intake Lipids (g/day) 66 (61–73) Days on PN 12 (8–15) Dextrose (g/day) 288 (275–303) AAs (g/day) 87 (84–90)	MCT/LCT 61 (54–67) 11 (7–15) 281 (273–301) 87 (83–92)

AA amino acids, *EN* enteral nutrition, *FO* fish oil, *ICU* intensive care unit, *LCT* long-chain triglycerides, *LOS* length of stay, *MCT* medium-chain triglycerides, *NR* not reported, *PN* parenteral nutrition

[a] Converted standard error mean (SEM) to standard deviation (SD)

sensitivity analysis was done excluding five RCTs that supplemented LCT + MCT in the control group [57, 58, 60, 61, 63, 64], ω-6-sparing strategies had no effect on mortality (RR 0.72; 95 % CI 0.43, 1.21; $P = 0.21$, heterogeneity $I^2 = 0$ %, see Fig. 2).

Secondary outcomes

Compared to LCT, when the RCTs reporting ventilator days were aggregated [57, 58, 60, 61, 63], overall ω-6 FA-sparing strategies were consistent with a reduction in duration of MV but differences were not statistically significant (WMD −2.57; 95 % CI −5.51, 0.37; $P = 0.09$, heterogeneity $I^2 = 25$ %) (Fig. 3). There was a trend towards a reduction in ICU LOS associated with the use of ω-6-sparing strategies when compared to LCT [53, 55, 57–61, 63] (WMD −2.31; 95 % CI −5.28, 0.66; $P = 0.13$, heterogeneity $I^2 = 68$ % (Fig. 4). When the data from five RCTs [57, 59, 61, 62, 64] that reported ICU-acquired infections were aggregated, ω-6-sparing strategy had no effect (RR 1.13, heterogeneity 95 % CI 0.87, 1.46; $P = 0.35$, heterogeneity $I^2 = 0$ %).

Subgroup analysis

LCTs plus MCT versus LCT emulsion

Four RCTs [53–56] compared LCTs plus MCT to an LCT emulsion. When statistically aggregated, these studies showed no difference in mortality (RR 0.84; 95 % CI 0.43, 1.61; $P = 0.59$, heterogeneity $I^2 = 0$ %) (Fig. 1). Only one trial [56] compared LCT + MCT to LCT that reported duration of ventilation and no significant differences were seen between the two groups. When the data from the two trials [53, 55] that report ICU LOS were aggregated, there were no differences in ICU LOS (WMD −1.46; 95 % CI −5.77, 2.85; $P = 0.51$, heterogeneity $I^2 = 78$ % (Fig. 4).

Fish oil-containing emulsions versus LCT or LCT + MCT

Four RCTs [60–63] comparing ω-3 oil-based LEs to an LCT or LCT + MCT reported mortality. When these data were aggregated, this strategy was not associated with a reduction in mortality (RR 0.76; 95 % CI 0.48, 1.21; $P = 0.25$ heterogeneity $I^2 = 0$ %) (Fig. 1). We found a trend towards a reduction in the duration of MV (WMD −1.81; 95 % CI −3.98, 0.36; $P = 0.10$, heterogeneity $I^2 = 0$ %) (Fig. 3). There were no differences between the groups in ICU LOS (WMD −1.13; 95 % CI −8.96, 6.69; $P = 0.78$; heterogeneity $I^2 = 78$ %) (Fig. 3) and infections (RR 0.79; 95 % CI 0.43, 1.43; $P = 0.43$, heterogeneity $I^2 = 0$ %).

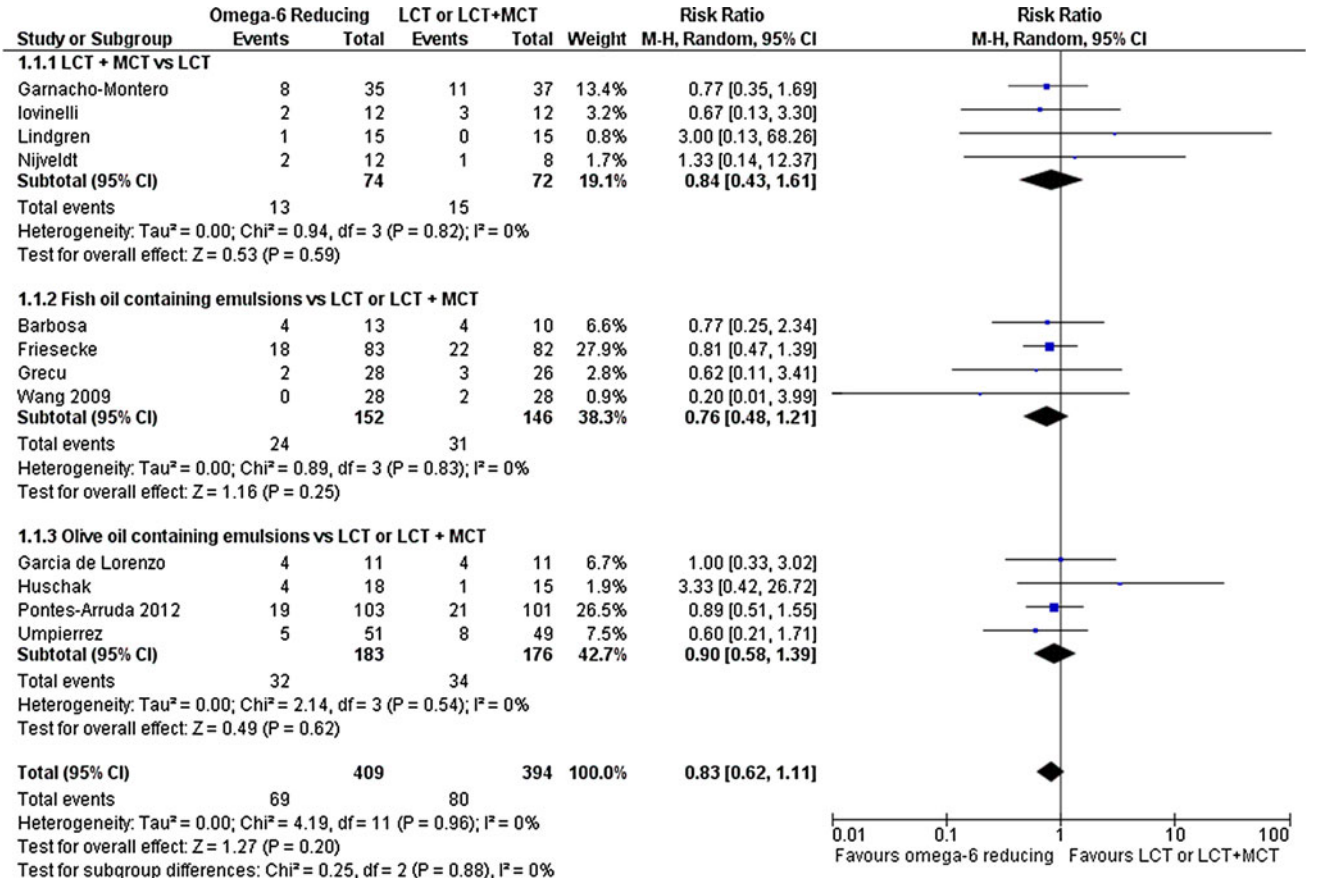

Fig. 1 Overall effect on mortality of LCT (ω-6) reducing strategy versus LCT + MCT. *LCT* long-chain triglycerides, *MCT* medium-chain triglycerides; *95 % CI* 95 % confidence intervals

ω-9 oil-based LEs versus an LCT + MCT mixture

Four RCTs [57–59, 64] compared an ω-9 oil-based LE to an LCT + MCT mixture. We did not find any difference between the groups in mortality (RR 0.90; 95 % CI 0.58, 1.39; $P = 0.62$, heterogeneity $I^2 = 0$ %) (Fig. 1); however, we found a significant reduction in the duration of MV (WMD −6.47; 95 % CI −11.41, −1.53; $P = 0.01$, heterogeneity $I^2 = 0$ %) (Fig. 2) but no effect on ICU LOS (WMD −4.08; 95 % CI −10.97, 2.81; $P = 0.25$, heterogeneity $I^2 = 59$ %) (Fig. 4). When three RCTs [57, 59, 64] that reported on ICU-acquired infections were aggregated, this strategy showed a tendency towards an increase in infections (RR 1.23; 95 % CI 0.92, 1.63; $P = 0.16$, heterogeneity $I^2 = 0$ %).

Risk of publication bias

There was no indication that publication bias influenced the observed aggregated results. Funnel plots were created for each study outcome (data not shown) and the tests of asymmetry were not significant for any outcome measure (mortality, $P = 0.48$; ICU LOS, $P = 0.88$; MV days, $P = 0.78$; and infections, $P = 0.29$).

Discussion

Our systematic review and meta-analysis is the first to evaluate the overall effects of parenteral ω-6-reducing strategies in the critically ill. When 12 eligible trials were statistically aggregated, we did not find statistically significant effects. However, the magnitude of the potential treatment effect, in terms of a reduction in mortality (relative risk reduction 17 %) and reduction in ICU LOS (more than 2 days less), if realized, would be consistent with a large and clinically and economically important difference. Furthermore, after removing the RCTs that utilized an LCT plus MCT-based strategy in the control group, we found that the magnitude of the effect increased with a 28 % relative risk reduction in mortality without achieving statistical significance. The lack of statistical precision is likely due to the small number of studies and the small sample size of each study. Given the

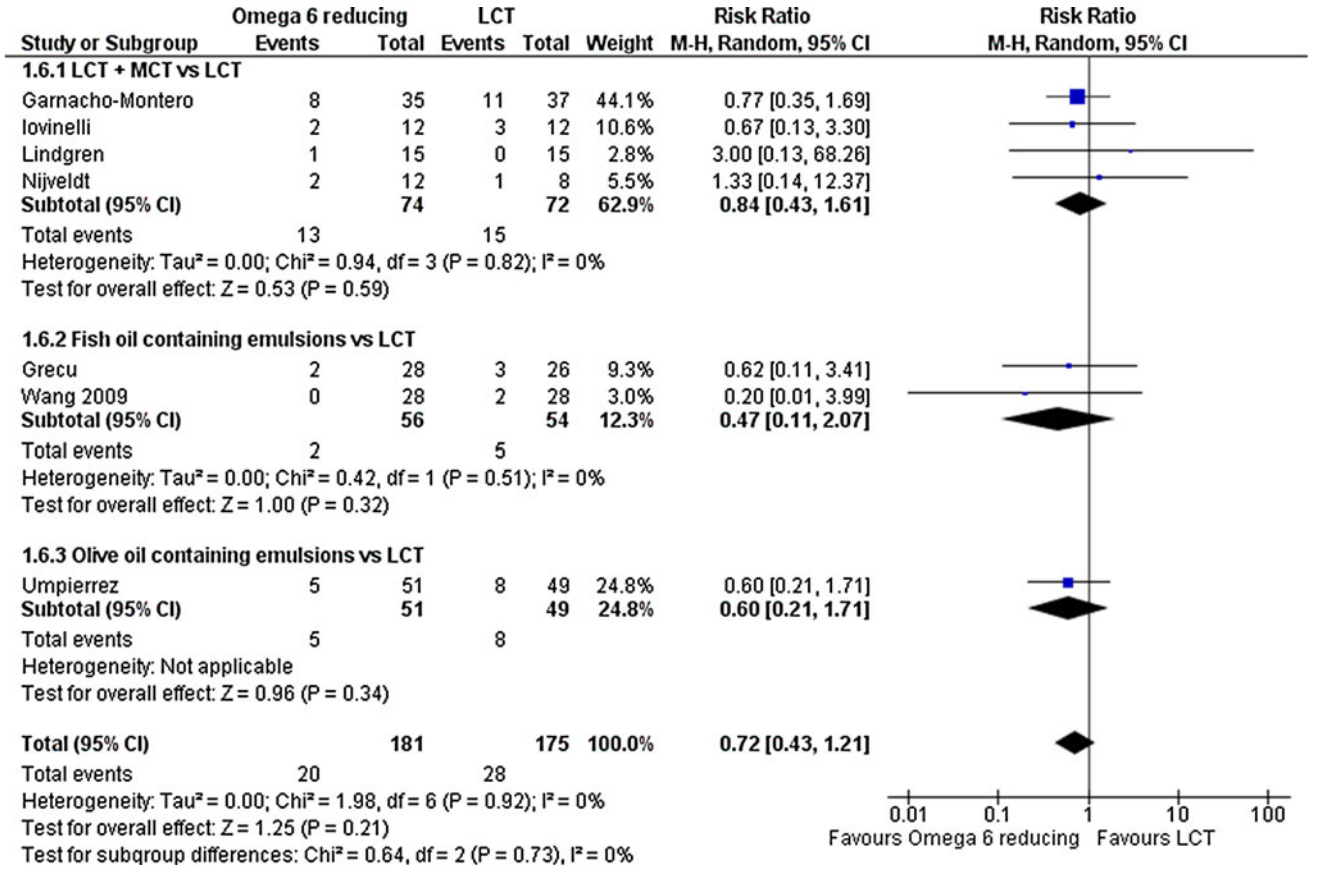

Fig. 2 Overall effect on mortality of LCT (ω-6) reducing strategy vs. LCT. *LCT* long-chain triglycerides, *MCT* medium-chain triglycerides, *95 % CI* 95 % confidence intervals

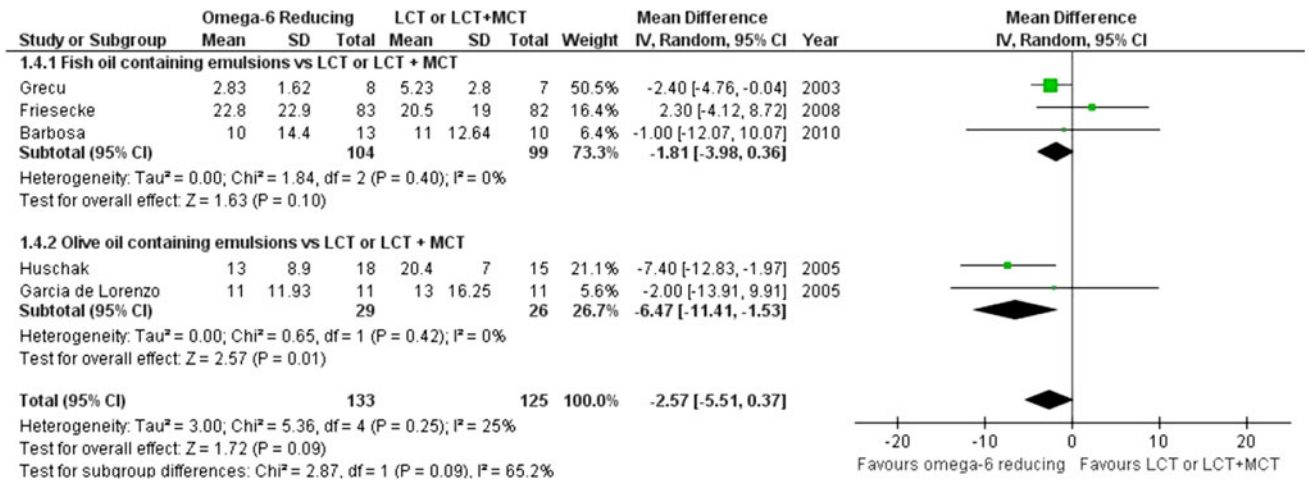

Fig. 3 Overall effect on ventilation days of ω-6-reducing strategy vs. LCT. *LCT* long-chain triglycerides, *95 % CI* 95 % confidence intervals, *SD* standard deviation

heterogeneous population of ICU patients included in this systematic review (sepsis, severe sepsis/septic shock, surgery, trauma, burns, and SIRS), the conclusions of our systematic review could be applied to a broad group of ICU patients. However, given the heterogeneity of alternative LEs, we explored several subgroups to evaluate if

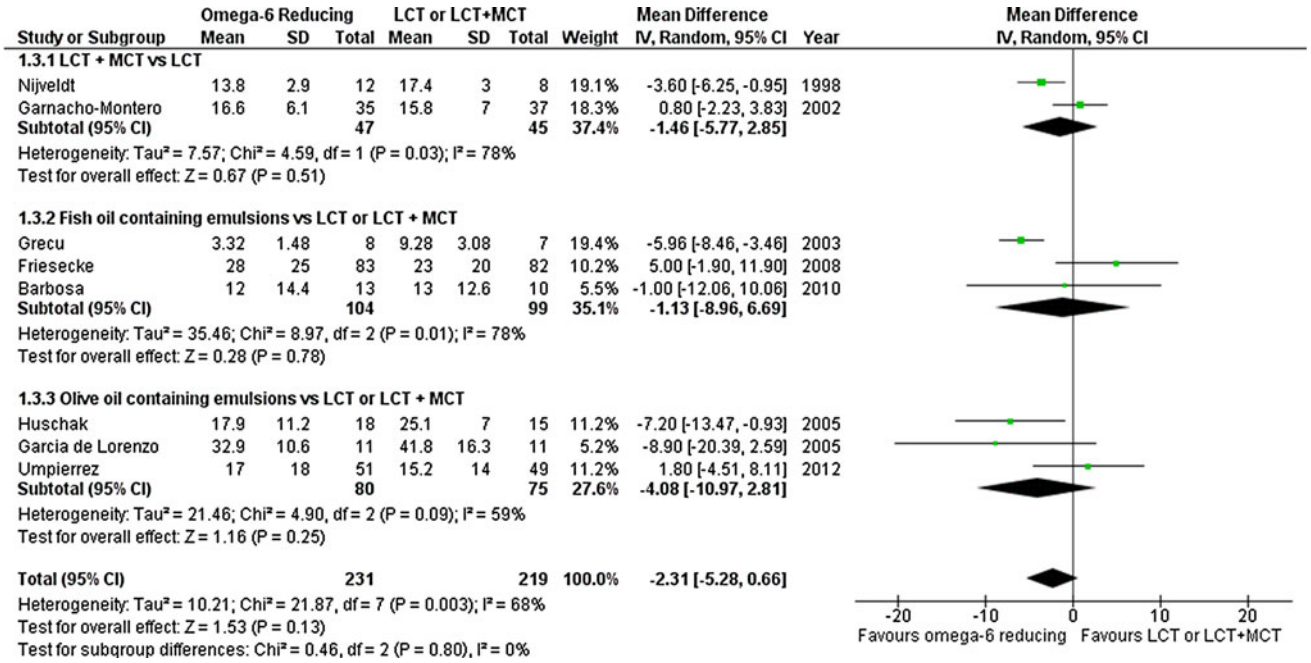

Fig. 4 Overall effect on ICU LOS of ω-6-reducing strategy vs. LCT. *LCT* long-chain triglycerides, *MCT* medium-chain triglycerides, *95 % CI* 95 % confidence intervals, *SD* standard deviation

the treatment effect was different across different commercial preparations. There are no head-to-head comparisons of these different alternative LEs strategies. Indirectly, by examining the risk ratios of the different alternatives, there does not appear to be any difference in the treatment effects. Therefore, we are unable to define the best ω-6-sparing strategy in the critically ill as available evidence on the differential effects of LEs in ICU patients remains limited after our meta-analysis.

Recently, two meta-analyses on parenteral FO have been published. In summary, all three reviews agree there is inadequate evidence to recommend the routine use of FO-containing emulsions in PN in the critically ill. Pradelli et al. [65] summarized 23 trials in elective surgery and critically ill patients and demonstrated that parenteral FO-enriched LEs were associated with a statistically and clinically significant reduction in infections (RR 0.61; 95 % CI, 0.45–0.84; $P = 0.002$) and the LOS, both in the ICU (MWD, −1.92; −3.27 to −0.58; $P = 0.005$) and in hospital (MWD, −3.29; −5.13 to −1.45; $P = 0.0005$), but no effect on overall mortality was shown (RR 0.89; 95 % CI 0.59, 1.33; $P =$ NS). More recently, Palmer et al. [66] statistically aggregated nine randomized trials of parenteral FO and showed no significant effect on mortality (RR 0.83; 95 % CI 0.57, 1.20; $P = 0.32$), infectious complications (RR 0.78; 95 % CI 0.43, 1.41; $P = 0.41$), and ICU LOS (MWD, 0.57; 95 % CI –5.05, 3.90; $P = 0.80$) in comparison with standard PN. These latter results are similar to our subgroup findings but in addition, we found a tendency toward a reduction in MV days associated with FO administration (WMD −1.81; 95 % CI −3.98, 0.36; $P = 0.10$). We believe that the difference between these two reviews and our subgroup analysis of FO administration was largely due to the difference in the papers included in the different reviews. Pradelli et al. [65] included ten trials in patients undergoing elective major abdominal surgery and not admitted to ICU ($N = 740$). Palmer et al. [66] included both papers published by Wang et al. in 2008 [29] and 2009 [62]. However, we excluded the 2008 Wang trial [29] because it did not include ICU patients and did not report on relevant clinical outcomes. In addition, we excluded two unpublished trials by Leiderman et al. [67] and Ignatenko et al. [68]. Both of these trials were included in the prior meta-analyses but are only published as abstracts and we were not able to obtain the data from the investigators necessary to have these trials included in our review.

The strength of our meta-analysis includes the fact that we used several methods to reduce bias (comprehensive literature search, duplicate data abstraction, specific criteria for searching and analysis) and have focused on clinically important primary outcomes for ICU patients. The major limitation of our meta-analysis was the small number of trials included, which may have resulted in statistical imprecision. Furthermore, the presence of heterogeneity, both clinical and statistical, weakens any inferences we can make from these data.

In spite of these limitations, we have demonstrated that alternative oil-based LEs in the critically ill may be able to reduce overall mortality and shorten ventilation days and ICU LOS. However, our study lacks the statistical precision to confirm these preliminary findings and further research is clearly warranted. Future trials should define the best mixture of lipids, target patient population, best timing, and duration of therapy to optimize the effects on underlying systemic inflammation, immune status, and metabolic processes while at the same time achieving an acceptable safety and tolerance profile.

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