frontiers

# *Supplementary Material*

**TABLE S1** Clinical Outcomes of Randomized Controlled Trials categorized as per Lipid Emulsion Formulation Type

| No | Cited Studies | Patient Type | *n* (IG/CG) | Control Group | Duration (days) | IIO* | NO* | CO* | Cellular FAC Changes* | Significant Outcomes* | Jadad Score† |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | **RCTs with Soybean Oil Lipid Emulsion (SOLE)** | | | | | | |
| 1 | Dionigi *et al*, 1985 | Malnourished GI cancer surgery | 8/7 | Lipid Free PN | 21 | +, - | NR | + | NR | ↑ PMN cells for IG group.<br>No change in IgG, IgM, C3c, Factor B for IG.<br>↓ sepsis score for IG. | **2** |
| 2 | Gogos *et al*, 1990 | Malnourished critically ill | 20/20 | Lipid Free PN | 10 | - | NR | NR | NR | ↓ ratio of helper to suppressor T cells for IG | **1** |
| 3 | Sedman *et al*, 1991 | Malnourished GI cancer surgery | 12/9 | Lipid Free PN | 7 | +, - | NR | NR | NR | ↓ LAK cell activity, ↑ IL-2 activity for IG. | **1** |
| 4 | Battisela *et al,* 1997 | Polytrauma | 30/27 | Lipid Free PN | 10 | NR | NR | - | NR | ↑ infections, ↑ ICU stay, ↑ hospital stay,<br>↑ duration MV for IG. | **2** |
| 5 | Furukawa *et al*, 2002 | Gastric, Colorectal esophageal surgery | 1717 | Lipid Free PN | 21 | - | - | NR | NR | ↑ IL-6 & ↑ CRP, ↓ lymphocyte proliferation in severe stress IG.<br>↑ Glucagon, cumulative NB negative in severe stress IG. | **2** |
| 6 | Monson *et al,* 1986 | Malnourished, septic, cancer surgery | 12/11 | Lipid Free PN | 14 | + | NR | NR | NR | ↑ IL2, ↑ T cells, & Helper T cells, ↑ ADCC function for IG. | **2** |
| 7 | Waitzberg *et al,* 1997 | Malnourished GI cancer surgery | 10/10 | Lipid Free PN | 2 | - | NR | NR | NR | ↓ bacteria killing mediated by neutrophils for IG. | **2** |

**TABLE S1** Continued

| No | Cited Studies | Patient Type | *n* (IG/CG) | Control Group | Duration (days) | IIO* | NO* | CO* | Cellular FAC Changes* | Significant Outcomes* | Jadad Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **RCTs with Physical Mixture MCT/LCT Lipid Emulsion** | | | | | | | | | | | |
| 8 | Sedman *et al*, 1991 | Malnourished GI cancer surgery | 12/12 | SOLE | 7 | + | NR | NR | NR | ↑ NK & ↑ LAK cell activity for IG. | **1** |
| 9 | Ball 1993 | Ventilated ICU | 10/10 | SOLE | 8 | NR | + | NR | NR | ↓ negative NB for IG | **1** |
| 10 | Jiang *et al*, 1993 | Abdominal surgery | 6/6 | SOLE | 10 | NR | +, - | NR | NR | ↓ Body Weight, ↑ insulin, ↓ TG, ↑ β hydroxybutyrate for IG | **1** |
| 11 | Smirniotis *et al*, 1998 | Post operative, ICU, sepsis, ARDS | 11/10 | SOLE | 1 | NR | NR | + | NR | ↑ oxygen consumption, $VO_2$ for IG. | **1** |
| 12 | Garnacho-Montero *et a*l, 2002 | ICU with sepsis | 26/26 | SOLE | 10 | NR | + | NR | NR | ↑ Retinol Binding Protein, ↑ insulin, improved NB for IG | **3** |
| 13 | Grau *et a*l, 2003 | Malnourished surgery & cancer | 26/31 | SOLE | 5 | NR | NR | + | NR | ↓ intra-abdominal infection for IG.<br>↓ mortality in IG group without cancer | **2** |
| 14 | Chen *et al*, 2005 | GI surgery | 15/15 | SOLE | 7 | NR | + | NR | NR | ↑ pre-albumin, ↑ insulin for IG | **2** |
| 15 | Iovinelli *et al*, 2007 | COPD on MV in ICU | 7/7 | SOLE | 15 | +,- | NR | + | NR | No change in immune markers for IG<br>↓ time of MV for IG | **2** |
| **RCTs with Structured Triglycerides Lipid Emulsion (STGLE)** | | | | | | | | | | | |
| 16 | Chambrier *et a*l, 1999 | Post abdominal surgery | 19/19 | MCT/ LCT | 5 | NR | + | NR | NR | No ↑ TG, No ↑ ASAT, No ↑ ALAT, NB positive for IG | **3** |
| 17 | Kruimel *et al*, 2001 | Postoperative aortic prosthesis | 12/13 | MCT/ LCT | 5 | NR | + | NR | NR | Improved cumulative NB, Less ↑ TG for IG | **4** |

**TABLE S1** Continued

| No | Cited Studies | Patient Type | *n* (IG/CG) | Control Group | Duration (days) | IIO* | NO* | CO* | Cellular FAC Changes* | Significant Outcomes* | Jadad Score† |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | Lindgren *et al*, 2001 | ICU | 9/11 | SOLE | 5 | NR | + | NR | NR | Improved cumulative NB for IG | **4** |
| 19 | Sandstrom *et al*, 1995 | Post abdominal surgery | 19/18 | SOLE | 6 | NR | +,- | NR | NR | ↑ carbon dioxide production, ↑ whole-body fat oxidation, ↑ Free Fatty Acid, ↑ plasma glycerol, ↑ 3-hydroxybutyric acid, with STGLE in part 2 | **4** |
| | | | | | **RCTs with Olive Oil Lipid Emulsion (OOLE)** | | | | | | |
| 20 | Vahedi *et al*, 2005 | Home parenteral nutrition with intestinal failure | 7/6 | SOLE | 90 | NR | NR | NR | + | ↑ Ɣ-LA, ↑ oleic acid, ↑ mead acid in plasma for IG | **4** |
| 21 | Onar *et al*, 2011 | Abdominal oncologic surgery | 10/10 | SOLE | 7 | NR | +,- | +,- | NR | ↑ ALP, ↑ GGT, ↑ total protein, ↑ albumin, ↓ total bilirubin for IG<br>No changes on catheter infections for IG | **3** |
| 22 | Demirer *et al*, 2016 | Elective GI surgery | 13/18 | MCT/LCT | 4 | NR | NR | + | NR | ↑ Weight, ↓ TBARS for IG | **1** |
| | | | | | **RCTs with Fish Oil Lipid Emulsion (FOLE)** | | | | | | |
| 23 | Morlion 1996 | Abdominal surgery | 10/10 | SOLE | 5 | NR | NR | NR | + | ↑ plasma phospholipid EPA, DHA and ALA for IG | **2** |
| 24 | Wachtler *et al*, 1997 | Major intestinal surgery | 20/20 | MCT/LCT | 5 | + | NR | NR | NR | ↑ $LTB_5$, ↓ $LTB_4$, ↓ $LTB_4/LTB_5$ ratio, ↓ TNF-α for IG | **3** |
| 25 | Roulet *et al*, 1997 | Elective total esophagectomy | 10/9 | SOLE | 7 | NR | NR | NR | + | ↑ EPA and EPA/AA in platelet phospholipids for IG | **2** |
| 26 | Linseisen *et al,* 2000 | Major abdominal cancer surgery | 17/16 | SOLE | 5 | NR | + | NR | + | ↑ α-tocopherol, ↓ Ɣ- tocopherol for IG<br>↑ plasma EPA, ↓ LA for IG | **3** |

**TABLE S1** Continued

| No | Cited Studies | Patient Type | *n* (IG/CG) | Control Group | Duration (days) | IIO* | NO* | CO* | Cellular FAC Changes* | Significant Outcomes* | Jadad Score† |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 27 | Weiss *et a*l, 2002 | Elective abdominal surgery | 12/11 | SOLE | 6 | + | NR | + | NR | ↓ IL-6, ↑ HLA-DR for IG<br>↓ post-operative stay on medical ward for IG | **2** |
| 28 | Schauder *et al*, 2002 | Large bowel surgery | 19/20 | SOLE | 6 | +,- | NR | NR | NR | ↑ IL-2, ↑ TNF, ↑ CD4/CD8 + for IG | **2** |
| 29 | Koller *et al*, 2003 | Elective abdominal surgery | 14/16 | SOLE | 5 | + | NR | NR | NR | ↑ in $LTB_5$, ↑ $LTB_5/LTB_4$ ratio for IG | **2** |
| 30 | Grimm *et al*, 2006 | Major abdominal surgery | 19/14 | SOLE | 5 | + | + | + | + | ↑ in $LTB_5$, ↑ $LTB_5/LTB_4$ ratio, ↑ α-tocopherol, ↓ length of hospital stay, ↑ total *n*-3 FA, ↑ plasma EPA & DHA, ↑ EPA/AA ratio, ↑ *n*-3:*n*-6 ratio for IG | **2** |
| 31 | Senkal *et al*, 2007 | Elective colorectal surgery | 19/21 | MCT/LCT | 5 | NR | NR | NR | + | ↑ EPA & DHA, ↑ *n*-3:*n*-6 ratio for IG | **5** |
| 32 | Wichmann *et al*, 2007 | Major abdominal surgery | 127/ 129 | SOLE | 5 | + | + | NR | NR | ↑ in $LTB_5$, ↑ $LTB_5/LTB_4$ ratio for IG<br>↑ α-tocopherol for IG | **3** |
| 33 | Liang *et al*, 2008 | Radical colorectal cancer surgery | 20/21 | SOLE | 7 | + | NR | NR | NR | ↓ IL-6, ↑ CD4+/CD8+ for IG | **5** |
| 34 | Berger *et al*, 2008 | Abdominal aortic aneurysm | 12/12 | MCT/LCT | 4 | NR | NR | NR | + | ↑ in EPA & DHA for IG | **3** |
| 35 | Piper *et al*, 2009 | Post abdominal surgery or cancer | 22/22 | OOLE | 5 | NR | + | NR | NR | ↓ AST, ↓ ALT, ↓ α-GST, ↓ TG for IG | 4 |

**TABLE S1** Continued

| No | Cited Studies | Patient Type | *n* (IG/CG) | Control Group | Duration (days) | IIO* | NO* | CO* | Cellular FAC Changes* | Significant Outcomes* | Jadad Score† |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 36 | Badia-Tahull *et al*, 2010 | Elective GI surgery | 13/14 | OOLE | 5 | NR | NR | + | NR | ↓ Infection rates for IG | **5** |
| 37 | Jiang *et al*, 2010 | GI/colonic cancer | 100/ 103 | SOLE | 7 | NR | NR | + | NR | ↓ SIRS, ↓ hospital stay for IG | **5** |
| 38 | Ma *et al*, 2012 | GI tumour surgery | 20/20 | MCT/LCT | 5 | NR | + | NR | NR | ↓ Low Density Lipoprotein for IG | **2** |
| 39 | Zhu *et a*l, 2012 | Colorectal cancer surgery | 29/28 | SOLE | 7 | +,- | NR | + | NR | ↓ CD4+/CD8+, ↓ IL-6, ↓ TNF- α for IG<br>↓ duration of SIRS, ↓hospital stay | **2** |
| 40 | Wang *et al*, 2012 | GI surgery | 32/32 | MCT/LCT | 5 | +,- | +,- | NR | NR | ↑ TNF-α, ↑ NF-K $\beta$ , ↑ $LTB_5/LTB_4$ ratio for IG<br>↑ APTT, ↓ total bilirubin for IG | **3** |
| 41 | Klek *et al*, 2013 | Intestinal failure | 34/39 | SOLE | 28 | NR | + | NR | + | ↓ AST, ↓ ALT ↓ total bilirubin, ↑ α-tocopherol for IG<br>↑ EPA & DHA in plasma & RBC, ↓ *n*-6:*n*-3 ratio for IG | **5** |
| 42 | De Miranda Torrinhas *et al*, 2013 | GI cancer | 31/32 | MCT/LCT | 3 | + | NR | NR | NR | ↓ IL-6, ↓ IL-10 for IG | **5** |
| 43 | Wu *et al*, 2014 | GI surgery | 20/15 | MCT/LCT | 5 | NR | + | NR | NR | Less ↑ TG & ↓ Glucose for IG | **2** |
| 44 | Ma *et al*, 2015 | Gastric, Colorectal cancer surgery | 45/41 | MCT/LCT | 8 | NR | + | NR | NR | Less ↑ TG, Less ↓HDL, Less ↓ Free Fatty Acid for IG | **5** |
| 45 | Demirer *et al*, 2016 | Elective GI surgery | 21/18 | MCT/LCT | 4 | NR | + | NR | NR | ↑ body weight, ↓ TBARS for IG | **1** |

**TABLE S1** Continued

| No | Cited Studies | Patient Type | *n* (IG/CG) | Control Group | Duration (days) | IIO* | NO* | CO* | Cellular FAC Changes* | Significant Outcomes* | Jadad Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 46 | Mayer *et al*, 2003 | Sepsis | 5/5 | SOLE | 10 | + | NR | NR | + | ↑ Neutrophil Inositol Phosphate, ↑ PAF, ↑ $LTB_5$, for IG<br>↑ respiratory burst for IG,<br>↑ EPA & DHA in plasma for IG | **1** |
| 47 | Mayer *et a*l, 2003 | Sepsis | 10/9 | SOLE | 5 | + | NR | NR | + | ↓ TNF-α, ↓ IL-1B, ↓ IL-6 and ↓ IL-8 for IG<br>↑ EPA & DHA in plasma & leukocytes for IG | **2** |
| 48 | Wang *et al*, 2008 | Acute pancreatitis | 20/20 | SOLE | 5 | + | NR | + | + | ↓ CRP, improvement in oxygenation index for IG<br>↓ CRRT days, ↑ plasma EPA for IG | **4** |
| 49 | Barbosa *et al*, 2010 | SIRS/Sepsis | 13/10 | MCT/LCT | 6 | + | NR | + | + | ↓ IL-6, ↓ IL-10, ↓ TNF-α, ↓ IL-1 $\beta$ for IG<br>↓ hospital stay, ↑ PO2/FiO2, ↑ EPA in plasma for IG | **3** |
| 50 | Sungurtekin *et al*, 2011 | SIRS/Sepsis | 10/10 | MCT/LCT | 7 | +,- | NR | NR | NR | ↑ IL-10, ↓ IL-6, ↓ TNF-α, ↓ IL-1 for IG with sepsis | **1** |
| 51 | Sabater *et al*, 2011 | ARDS | 8/8 | SOLE | 12 hours | + | NR | NR | NR | ↓ LTB4 for IG | **2** |
| 52 | Han *et al*, 2012 | Surgical ICU | 18/12 | MCT/LCT | 7 | + | NR | NR | NR | ↓ IL-1, ↓ IL-8, ↓ IFN-Ɣ, ↓ IL-6, ↓ TNF-α for IG | **5** |
| 53 | Gultekin *et al*, 2014 | Sepsis | 16/16 | OOLE | 5 | + | + | NR | NR | ↓ LTB4, ↓ CRP, ↑ albumin for IG | **3** |
| 54 | Metry *et al*, 2014 | Post-surgery ICU | 41/42 | SOLE | 7 | + | NR | NR | NR | ↓ IL-6 for IG | **5** |
| 55 | Grau-Carmona *et al*, 2015 | ICU | 81/78 | MCT/LCT | 5 | NR | NR | + | NR | ↓ nosocomial infections, ↑ predicted time free of infection for IG | **5** |

**TABLE S1** Continued

| No | Cited Studies | Patient Type | *n* (IG/CG) | Control Group | Duration (days) | IIO* | NO* | CO* | Cellular FAC Changes* | Significant Outcomes* | Jadad Score† |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 56 | Chen *et al,* 2017 | Sepsis | 41/37 | SOLE | 7 | NR | NR | + | NR | ↓ 60 day mortality for IG | **3** |
| 57 | Bohnert *et al*, 2018 | Home Parenteral Nutrition | 15/18 | MCT/LCT | 56 | - | - | - | + | ↑ EPA, ↑ DHA, ↑ DPA in erythrocytes, platelets, serum phospholipids for IG | **5** |

*AA, Arachidonic Acid; ADCC, Antibody-dependent cellular cytotoxicity; ALA, Alpha Linolenic Acid; ALAT, Alanine aminotransferase; ALP, Alkaline phosphatase; ALT, Alanine transaminase; APTT, Activated Partial Thromboplastin Time; ASAT/AST, Aspartate aminotransferase; CD4/CD8+, T4 helper cells/T8 suppressor cells; CG, Control Group; CO, Clinical Outcome; CRP, C-Reactive Protein; CRRT, Continuous Renal Replacement Therapy; DHA, docosahexaenoic acid; DPA, Docosapentaenoic acid; EPA, Eicosapentaenoic acid; FAC, Fatty Acid Composition; GGT, Gamma-Glutamyl Transferase; GI, Gastrointestinal; GST, Glutathione S-transferase; HLA-DR, Human Leukocyte Antigen-antigen D related;ICU, intensive care unit; IFN, Interferon; Ig, Immunoglobulin; IG, Intervention Group; IIO, Immuno-Inflammatory Outcome; IL, Interleukin; LA, Linoleic Acid; LAK, Lymphokine Activated Killer; $LTB_4$, Leukotriene $B_4$; $LTB_5$, Leukotriene $B_5$; MV, Mechanical Ventilation; NB, Nitrogen Balance; NF-Kβ,nuclear factor-kB; NK, Natural Killer; NO, Nutrition Outcome; PAF, Platelet Activating Factor; PMN, Polymorphonuclear; PN, Parenteral Nutrition; PO2/FiO2, partial pressure of oxygen/fraction of inspired oxygen; SIRS, Systemic Inflammatory Response Syndrome; TBARS, Thiobarbituric Acid Reactive Substances; TG, Triglyceride; TNF, Tumour Necrosis Factor.*

**Footnote:**

*"+",benefit; "-",risk'; NR, Not Reported; "↓", significantly reduced; "↑", significantly increased.

†Jadad Score an instrument used to limit the risk of introducing bias and assess quality of RCTs. Scoring was given based on RCTs described as randomized, double-blinded and withdrawals or drop-outs were stated. Additional points were given if method to generate the sequence of randomization and double-blinding was described and it was appropriate. However points will be deducted if the method to generate the sequence of randomization and double-blinding was described but was inappropriate. Additionally if withdrawals were not mentioned, no points will be given. High quality RCTs are scored at 4- 5 and low quality at 1-2.