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ORIGINAL RESEARCH

Infectious Disease

Lipid intensive drug therapy for sepsis pilot: A Bayesian phase I clinical trial

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Abstract

Objectives: Cholesterol may be protective in sepsis. Patients with early sepsis may have critically low cholesterol levels that are associated with poor outcomes. The study objective was to test the safety of a fish oil–containing lipid injectable emulsion for stabilizing early cholesterol levels in sepsis.

Methods: Phase I Bayesian optimal interval design trial of adult patients with septic shock (Sequential Organ Failure Assessment score ≥4 or vasopressor dependence). Using sequential dose escalation, participants received 2 doses of 1.0 to 1.6 g/kg of lipid emulsion (Smoflipid 20% lipid emulsion) within 48 hours of enrollment. Cholesterol levels, function, and organ failure were assessed serially during the first 7 days of hospital admission.

Measurements and Main Results: A total of 10 patients with septic shock were enrolled. One patient withdrew for social reasons. Another patient had an unrelated medical complication and received 1 drug dose. Of 9 patients, mean age was 58 years (SD 16), median Sequential Organ Failure Assessment was 8, and 28-day mortality was 30%. No serious adverse events related to lipid infusion occurred. The six occurrences of non-serious adverse events possibly related to lipid infusion included hyperglycemia (1), elevated triglycerides (3), anemia (1), and vascular access redness/pain (1) for all

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doses. The mean change in total cholesterol levels from enrollment was −7 (SD 16.6) at 48 hours and 14 (SD 25.2) at 7 days.

Conclusions: Fish oil–containing lipid emulsion administration during early septic shock was safe. Further studies are needed to assess effects on cholesterol levels, function, and organ failure.

Clinical Trial Registration: NCT03405870.

KEYWORDS

cholesterol, lipid emulsion, lipids, organ failure, parenteral nutrition, sepsis, septic shock

1 | INTRODUCTION

1.1 | Background

Sepsis is a life-threatening dysregulated host response to infection that leads to organ failure and potential death.[1] Both high-density lipoprotein (HDL-C) and low-density lipoprotein cholesterol (LDL-C) have been shown to have protective roles in sepsis.[2–9] In addition to sepsis causing well-described immunologic derangements,[10–12] metabolic dysregulation has direct effects on lipid metabolism,[13,14] demonstrated by changing levels of HDL-C, LDL-C, and triglycerides that strongly predict clinical outcomes in early sepsis including organ failure and death.[3,13,15–18]

The mechanisms for the downward trends in HDL-C and LDL-C that predict poor outcomes in sepsis have not been explained. One study of sepsis patients found that a rare missense single nucleotide polymorphism in cholesteryl ester transfer protein, which functions to transport cholesteryl esters between HDL-C and lower density lipoproteins (LDL-C, very low-density lipoprotein cholesterol, and triglycerides), was associated with lower HDL-C levels and lower survival, more organ failure, and a greater need for organ support compared with non-carriers.[19] In another study, reduced levels of lecithin cholesterol acyltransferase (responsible for HDL-C maturation) and cholesteryl ester transfer protein inversely correlated with C-reactive protein and lipopolysaccaride levels.[20] Catecholamines, cortisol, and growth hormone during sepsis stimulate adipose tissue lipolysis that may result in increased levels of very low-density lipoprotein cholesterol and triglycerides.[3,21,22]

1.2 | Importance

Certain exogenous lipids may be beneficial in sepsis. Fish oils, which contain protective, anti-inflammatory omega-3 fatty acids, have been shown to be beneficial in some studies, although the literature is conflicting.[23–27] Preclinical data have shown that fish oil lipid emulsions can reduce acute kidney and acute lung injury, suppress inflammation, and favorably modulate immune function in septic mice.[28–30] There are 4 main mechanisms for the potential protective effects of omega-3 fatty acids in sepsis: (1) metabolism into anti-inflammatory eicosanoid inflammatory mediators, (2) alteration of membrane lipid rafts, (3) inhibition of nuclear receptor activation (nuclear factor-κB) to modulate inflammatory mediator production, and (4) metabolism into novel pro-resolving/anti-inflammatory mediators (resolvins, protectins, and maresins). Resolvins, protectins, and maresins that are metabolized to spontaneous proresolving mediators can be conceptualized as inflammation "shut-off valves" in sepsis.[31]

Exogenous administration of omega-3 fatty acids may help overcome the massive inflammatory response that occurs during sepsis. A recent randomized controlled trial of 60 ICU sepsis patients demonstrated a significant improvement in organ failure after intravenous administration of 10% fish oil.[24] Omega-3 fatty acids have also been shown to improve several critical HDL functions including HDL-ApoA-I-exchange,[32,33] reverse cholesterol transport,[34–37] and antioxidant functions of HDL and paraoxonase-1 (PON-1) activity.[34] Finally, fish oil lipid emulsions may safely elevate cholesterol levels.[38] Because lipid emulsions have a large proportion of triglycerides, its greatest effect will likely be the elevation of triglycerides and LDL-C that have greater cholesterol content.

1.3 | Goals of this investigation

Based on previous studies, we hypothesized that early administration of a fish oil–containing lipid injectable emulsion may have up to 3 beneficial effects in sepsis and septic shock patients: (1) lipid substrate for cholesterol synthesis to increase cholesterol levels, (2) anti-inflammatory lipids to mitigate organ dysfunction, and (3) improved HDL antioxidant function. Therefore, we designed a phase I clinical trial of lipid emulsion therapy in sepsis and septic shock patients to test drug safety and tolerability. Changes in early cholesterol levels (enrollment to 48 hours) and effects on HDL antioxidant function were measured as secondary exploratory end points.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

Written informed consent was obtained from all participants or their legal representatives. The study was approved by the University of

Florida College of Medicine Institutional Review Board. All ethical procedures were upheld in the conduct of this study. The US Food and Drug Administration approved the off-label use of the study drug in sepsis patients. Safety monitoring occurred under the oversight of a safety monitor. Study oversight was provided by a data safety monitoring board (DSMB). Patients were enrolled in the study from August 2019 until April 2020.

The study protocol has been previously published and registered (NCT03405870).[39] Briefly, this was a phase I, sequential, dose-escalation study of lipid emulsion therapy (Smoflipid, Fresenius Kabi, Homburg, Germany) with a Bayesian optimal interval (BOIN) design. Each 100 mL of Smoflipid contains ≈6 g soybean oil, 6 g medium chain triglycerides, 5 g olive oil, 3 g fish oil, 1.2 g egg phospholipids, 2.5 g glycerin, 16.3 to 22.5 mg all-rac-α-tocopherol, 0.3 g sodium oleate, water for injection, and sodium hydroxide for pH adjustment (pH 6–9). The BOIN design was chosen for the ability to set a lower dose-limiting toxicity (DLT) threshold of 10%, allowing for superior safety compared with the classic 3 + 3 phase I trial (30% DLT rate).[40] The BOIN design is a newer class of phase I trial designs that determines the dose transition based on the observed toxicity rate at a current dose (number of patients who experienced toxicity divided by total number treated) and with respect to a prespecified toxicity tolerance interval. If the observed toxicity rate is located within the interval, the current dose is retained. However, if the observed toxicity rate is above the upper boundary of the interval, the dose is deescalated; if the observed toxicity rate is smaller than the lower boundary of the interval, the dose is escalated.[41] By using fixed boundaries, the BOIN design is simpler and more flexible than the 3 + 3 design. It does not impose the requirement that patients treated at 1 dose cannot exceed 6 patients. It also allows investigators to set a clinically relevant toxicity threshold based on relevance to a specific condition and investigational drug. Planned enrollment was for 16 patients or fewer (depending on the observed rate of DLTs) to evaluate safety and tolerability.

Smoflipid was chosen because of the anti-inflammatory fish oil component balanced with other lipids for cholesterol synthesis. The dose ranges were based on manufacturer recommended and US Food and Drug Administration–approved dosing for nutritional purposes. Drug doses started at 1.0 g/kg and then increased incrementally by 0.2 g/kg in groups of 2 patients. Dose escalation or de-escalation occurred based on observance of DLTs at a specific dose.[42]

2.2 | Selection of participants

2.2.1 | Inclusion criteria

Eligible patients were at least 18 years of age with a primary diagnosis of sepsis (within 24 hours of recognition) based on sepsis-3 definitions.[1] Patients were required to have sepsis with moderate organ failure (Sequential Organ Failure Assessment Score [SOFA] ≥ 4) or vasopressor use. A screening lipid panel was drawn and paid for by the study, and only patients with a total cholesterol level ≤100 mg/dL or HDL-C + LDL-C ≤ 70 mg/dL were eligible. Lipid panels were added on to preliminary laboratory tests whenever possible.

The Bottom Line

Metabolic derangements in sepsis are a hot topic in sepsis research. The objective of this pilot study, that is, a phase I trial to assess safety and tolerability of Smoflipid emulsion in 2 sequential escalating doses in selected patients with sepsis, is shown to assess the safety of a fish oil–containing injectable emulsion as a treatment for stabilizing cholesterol levels.

2.2.2 | Exclusion criteria

Patients were excluded from the study for any of the following: (1) total bilirubin >2 mg/dL; (2) serum albumin <1.5 mg/dL; (3) hypersensitivity to fish, egg, soybean, peanut protein, or any of the active ingredients or excipients; (4) severe hyperlipidemia or severe disorders of lipid metabolism with serum triglycerides >400 mg/dL, (5) alternative/confounding diagnosis causing shock or critical illness (eg, myocardial infarction or pulmonary embolus, massive hemorrhage, trauma); (6) significant traumatic brain injury (evidence of neurologic injury on computed tomography scan and a Glasgow Coma Scale < 8); (7) refractory shock (likely death within 12 hours); (8) advanced directives restricting aggressive care or treating physician deems aggressive care unsuitable; (9) anticipated requirement for surgery that would interfere with drug infusion; (10) severe primary blood coagulation disorder (protein C, protein S deficiency, or antithrombin deficiency; antiphospholipid antibodies); (11) acute pancreatitis accompanied by hyperlipidemia; (12) acute thromboembolic disease; (13) uncontrollable source of sepsis (eg, irreversible disease state such as unresectable dead bowel); (14) severe immunocompromised state; (15) pregnancy or lactation; (16) concurrently receiving intravenous lipid formulations (eg, parenteral nutrition, propofol); (17) child Pugh class B/C liver disease; or (18) actively on extracorporeal membrane oxygenation or anticipated need for extracorporeal membrane oxygenation within 48 hours of enrollment.

2.3 | Interventions

All study participants were treated with an institutional standard care bundle for sepsis.[43] Consented participants were enrolled sequentially in groups of 2 patients per dose. Enrollment was planned until the maximum tolerated dose or the maximum planned drug dose was achieved. The specified dose of study drug was administered twice during the first 48 hours after enrollment at 24-hour intervals so that each patient received 2 doses of the drug at each dose level. Study monitoring was performed in accordance with the study protocol.[39] To meet the requirement for protocol completion, participants must have received both doses of lipid emulsion during the first 48 hours after enrollment and have a 48-hour lipid panel and research blood drawn.

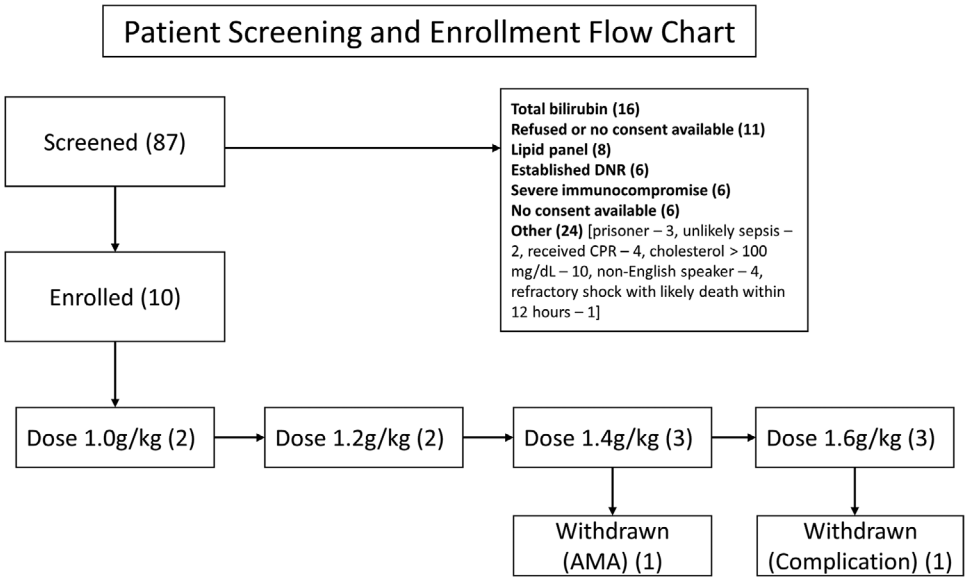

FIGURE 1 Patient screening and enrollment flow chart. AMA, against medical advice; CPR, cardiopulmonary resuscitation; DNR, do not resuscitate

2.4 | Measurements

Blood was drawn for cholesterol levels, HDL antioxidant function, and SOFA score on enrollment, after 48 hours, and on day 7. Lipids panels were drawn on enrollment; at 24, 48, and 72 hours; and on day 7. HDL testing included dysfunctional HDL using the cell-free assay (reported as HDL inflammatory index [HII]), and the PON-1 enzyme assay, a main antioxidant enzyme on HDL, as in previous studies.[44]

2.5 | Outcomes

The primary end point was safety determined by serious reactions as well as the maximum tolerated dose (the dose at which >10% of patients experience a predefined DLT). Predefined serious reactions included shortness of breath, hypoxia, respiratory distress, fat overload[45] (headache, fever, jaundice, hepatosplenomegaly, respiratory distress, hemorrhage), or significant hepatitis not attributed to sepsis or septic shock. Non-serious adverse reactions were also recorded. Secondary end points included change in cholesterol levels and SOFA score from enrollment to 48 hours and 7 days, in-hospital mortality, 28-day mortality, and HDL antioxidant function.

2.6 | Analysis

Demographics, cholesterol levels, lipid oxidation status, and SOFA score data were presented using descriptive statistics with means and SDs for normally distributed data and medians and interquartile ranges (IQRs) for non-normally distributed data. For serious reactions and adverse events (AEs), categorical data were presented as frequencies and percentages.

3 | RESULTS

3.1 | Characteristics of the study participants

There were 87 patients screened for enrollment, and 10 patients enrolled. The most common study exclusions were elevated bilirubin, refusal or lack of an available legal representative to provide consent, and lipid panel results not meeting criteria (Figure 1). One patient withdrew himself from the study and left the hospital against medical advice before completion of the day 1 infusion for social reasons. Another patient completed the first dose of study drug, but had a medical complication deemed not related to the study drug by the safety monitor and was not administered a second dose of drug (see Safety section). The mean age for the 9 patients was 58 years (SD 15.7), with 6 male (66%) and 3 (33%) female patients and 6 (66%) White patients and 3 (33%) Black patients. Mortality at 28 days was 33% (3/10). Descriptive characteristics are presented in Table 1.

For the 9 included patients (excluding the patient who withdrew from the study), there were 4 who were on baseline statin use before hospitalization, and 3 continued on statins while hospitalized. A total of 6 patients received enteral nutrition while hospitalized (Table 2).

3.2 | Main results

3.2.1 | Safety

There were no serious reactions to the study drug as determined by the safety monitor and the DSMB. The one patient withdrawn for a medical complication was found to have a displaced percutaneous gastrostomy tube through which enteral feeds had been administered the

TABLE 1 Demographics and participant characteristics

Characteristics	Median (Q1, Q3) or N (%)
Age, y	64 (57, 68)
Baseline GCS	15.00 (15, 15)
Systolic blood pressure, mmHg	87 (71, 117)
Diastolic blood pressure, mmHg	57 (47, 70)
Heart rate, beats/min	103 (97, 135)
Respiration rate, breaths/min	20 (18, 24)
Temperature, F	98.8 (98.2, 99.5)
Oxygen saturation, %	97 (94, 98)
Initial lactate level, mmol/L	3.5 (2.1, 4.1)
Repeat lactate level, mmol/L	3.7 (2.1, 5.8)
SOFA score	8 (7, 11)
Sex	
Male	5 (56)
Female	4 (44)
Race	
White	6 (67)
Black	3 (33)
Comorbidities	
Diabetes mellitus	5 (56)
COPD	1 (11)
Active cancer	1 (11)
Indwelling vascular line	1 (11)
Nursing home resident	2 (22)
Mortality	3 (33)
Receiving vasopressors	9 (100)
Confirmed source of infection	
Pulmonary	4 (40)
Urinary tract[b]	2 (20)
Intra-abdominal	1 (10)
Skin/soft tissue[a]	1 (10)
Blood	3 (30)

COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment Score.
[a] Patient with multiple sources of infection.
[b] Patient with two sources of infection.

day after enrollment. The 24-hour lipid panel showed triglyceride levels >400 mg/dL and peritonitis, and the patient was emergently taken to the operating room for laparotomy and washout. The safety monitor made the recommendation to the principal investigator that a second dose of the study drug should not be administered, and the patient was withdrawn. After in-depth case review, the DSMB determined that the hypertriglyceridemia was not attributed to the study drug.

Of the 10 enrolled patients, there were 3 deaths attributed to septic shock or related complications. One patient in the 1.0 g/kg group died after the second dose of study drug and before the 72-hour end point; therefore, the lipid date was reported after 48 hours. No deaths were temporally related to the drug infusions. AEs were any unfavorable and unintended sign, symptom, or disease temporally associated with the use of Smoflipid in this study. There were 6 AEs that were possibly related to the lipid infusion (Table 3). The most common AE was elevated blood triglycerides. AEs were only considered DLTs if they met the predefined study protocol criteria. None of the reported AEs were classified as DLTs.

3.3 | Secondary results

3.3.1 | Quantitative lipid measures

Mean enrollment and 48-hour and 7-day total cholesterol, HDL-C, LDL-C, and triglyceride levels are presented in Tables 4 and 5. The mean change in total cholesterol levels from enrollment to 48 hours (48 hours − enrollment) was −7 (SD 16.6) and from enrollment to 7 days (7 days − enrollment) was 14 (SD 25.2). Graphical representations of lipid levels over time are presented in Supplemental Digital Content 1.

3.3.2 | Qualitative lipid measures

PON-1 enzymatic activity varied over time for all participants. In general, greater PON-1 activity is an indicator of improved HDL antioxidant function. Patients who received 1.0 and 1.4 g/kg had higher initial PON-1 activity levels, which decreased over time, although the 1.4 g/kg group had less of a reduction in PON-1 activity. The 1.2 and 1.6 g/kg groups both had PON-1 levels that started low and stayed low through day 7. All patients had pro-inflammatory HDL as indicated by HII > 1. Patients who received 1.0, 1.2, and 1.6 g/kg had HII levels that started higher and improved by day 7, although the 1.6 g/kg had increased HII at 48 hours compared with enrollment. Patients in the 1.4 g/kg group had HII levels that increased from enrollment to day 7 despite improved HII at 48 hours. PON-1 and HII data are presented in Supplemental Digital Content 2 and are graphically presented in Supplemental Digital Content 3.

3.3.3 | Organ failure

The median SOFA score at enrollment was 8 (IQR, 7–11), at 48 hours was 10 (IQR, 5–11), and at 7 days was 3 (IQR, 1–6.25). The mean change from enrollment SOFA to 48 hours (48 hours − enrollment) was −1 (SD 4.2), and from enrollment to day 7 was −4 (SD 6.2).

3.3.4 | DSMB determinations

The DSMB met 3 times during the conduct of the study: after the enrollment of the first 2 patients, the first 4 patients, and the first 10 patients. After reviewing the data at the third meeting, including incidence of AEs, protocol deviations, and dose-response curves,

TABLE 2 Statin use and enteral nutrition

Age, y	Sex	Smoflipid dose	Baseline statin use	In-hospital statin use	Enteral nutrition intake	Fat content	Dietary supplements
64	F	1.0 g/kg	No	No	NA	NA	NA
68	M	1.0 g/kg	Yes	No	NA	NA	Pro-stat
75	M	1.2 g/kg	Yes	Yes	Novasource Renal	23.8 g/237 mL	Pro-stat
31	M	1.2 g/kg	No	No	NA	NA	Boost, Ensure
72	F	1.4 g/kg	Yes	Yes	Diabetisource AC	14.7 g/250 mL	Pro-stat
34	M	1.4 g/kg	No	No	Peptamen	10 g/250 mL	Pro-stat
57	M	1.6 g/kg	No	No	Novasource Renal, Nutren 1.5 Cal	23.8 g/237 mL	Pro-stat
65	F	1.6 g/kg	Yes	Yes	Novasource Renal, Nutren 1.5 Cal	23.8 g/237 mL	NA
59	F	1.6 g/kg	No	No	Isosource	10 g/250 mL	NA

F, female; M, male; NA, not available.

TABLE 3 Adverse events of study participants by dose

	Adverse events[a]				Unrelated serious adverse events
Dose	Hyperglycemia	Increased blood triglycerides	Anemia	Vascular access redness, pain, or swelling	Death
1.0 g/kg	1	1	1	0	1
1.2 g/kg	0	2	0	0	0
1.4 g/kg	0	0	0	0	0
1.6 g/kg	0	0	0	1	2
Total	1	3	1	1	3

[a] Adverse events were any unfavorable and unintended sign, symptom, or disease temporally associated with the use of Smoflipid in this study. Adverse events were only considered dose-limiting toxicities if they met the predefined study protocol criteria. None of the these were classified as dose limiting or serious.

feasibility issues were discussed. Specifically, the increasing weight-based dosing of the study drug resulted in increasing lengths of drug infusions (16 hours at 1.6 g/kg) as well as greater potential for hypertriglyceridemia and catheter infiltrations. As there did not appear to be a clear dose-response relationship to increasing doses of the study drug and cholesterol levels and given the feasibility issues with longer infusion times, the DSMB recommended concluding the phase I study at a maximal dose of 1.6 g/kg body weight. No patients received the maximal planned dose of 1.8 g/kg.

3.4 | Limitations

The main limitation to this study was the small sample of patients; however, this is not uncommon among phase I trials. Stringent enrollment criteria limited patient enrollment in this study. In particular, the exclusion of patients with elevated bilirubin given the drug's hepatic metabolism and risk of complications limited the number of patients who could be enrolled. Also, narrow inclusion criteria were needed to safely study DLTs in critically ill patients with septic shock given the

TABLE 4 Lipid panel statistics for study participants

Cholesterol (mg/dL)	T0/1H	T24H	T48H	T72H	T7D	T48H–T0/1H	T7D–T0/1H
Total cholesterol, median (Q1, Q3)	78 (74, 85)	62 (51, 88)	70 (58, 87)	80 (72, 106)	99 (88, 110)	−8 (−21, 4)	19 (9, 25)
HDL-C, median (Q1, Q3)	36 (22, 37)	18 (12, 20)	15 (11, 22)	15 (13, 18)	18 (15, 24)	−5 (−24, −1)	−4 (−23, 2)
LDL-C, median (Q1, Q3)	19 (17, 23)	13 (9, 18)	20 (11, 26)	36 (26, 46)	48 (43, 54)	3 (−15, 5)	27 (20, 31)
Triglycerides, median (Q1, Q3)	123 (69, 211)	148 (100, 380)	146 (124, 244)	172 (122, 228)	146 (132, 156)	24 (−4, 55)	13 (−21, 45)

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; T0/1H, time of enrollment; T24H, 24 hours after enrollment; T48H, 48 hours after enrollment; T72H, 72 hours after enrollment; T7D, 7 days after enrollment.

TABLE 5 Lipid panel statistics for study participants by dose

Cholesterol variable (mg/dL)	T0/1H (mean ± SD)	T24H (mean ± SD)	T48 (mean ± SD)	T72H (mean ± SD)	T7D (mean ± SD)
1.0 g/kg					
Total cholesterol	78 ± 11.3	77 ± 21.2	66 ± 11.3	70 ± NA	90 ± NA
HDL-C	28 ± 11.3	30 ± 30.4	23 ± 21.2	9 ± NA	14 ± NA
LDL-C	18 ± 2.8	2 ± 34.6	6 ± 7.1	18 ± NA	45 ± NA
Triglycerides	158 ± 126.6	224 ± 219.9	184 ± 84.9	215 ± NA	156 ± NA
1.2 g/kg					
Total cholesterol	80 ± 5.7	92 ± 4.9	96 ± 4.9	110 ± 3.5	98 ± 15.6
HDL-C	18 ± 4.9	14 ± 3.5	16 ± 7.8	18 ± 6.4	21 ± 4.2
LDL-C	18 ± 2.1	8 ± NA	34 ± 17.7	50 ± 27.6	46 ± 12.7
Triglycerides	221 ± 14.7	372 ± 41.7	224 ± 74.2	206 ± 88.4	154 ± 118.8
1.4 g/kg					
Total cholesterol	82 ± 10.6	68 ± 27.6	72 ± 20.5	89 ± 24.0	102 ± 18.4
HDL-C	38 ± 0.7	32 ± 19.1	25 ± 15.6	24 ± 14.1	26 ± 14.8
LDL-C	20 ± 4.7	18 ± 2.1	24 ± 6.4	42 ± 7.8	48 ± 3.5
Triglycerides	119 ± 31.1	89 ± 32.5	115 ± 8.5	118 ± 10.6	146 ± 2.1
1.6 g/kg					
Total cholesterol	76 ± 10.1	54 ± 6.1	58 ± 15.9	69 ± 20.1	85 ± 53.4
HDL-C	34 ± 10.1	15 ± 6.4	12 ± 7.4	12 ± 7.2	16 ± 11.8
LDL-C	26 ± 9.8	12 ± 2.1	2 ± 34.1	33 ± 15.6	42 ± 47.6
Triglycerides	79 ± 37.9	233 ± 190.3	218 ± 127.0	238 ± 151.6	134 ± 27.5

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not available. T0/1H, time of enrollment; T24H, 24 hours after enrollment; T48H, 48 hours after enrollment; T72H, 72 hours after enrollment; T7D, 7 days after enrollment.

severity of illness and potential risk to the patients. Another limitation to enrollment was lack of available consent, given our inner-city, underserved patient population. Many patients did not have family available at the bedside to provide consent.

4 | DISCUSSION

In this phase I clinical trial of fish oil–containing lipid injectable emulsion therapy in patients with sepsis and septic shock, there were no serious reactions related to drug infusion. There were 6 adverse events, none of which were serious or life-threatening. One patient experienced a medical complication that was not related to the drug infusion and was withdrawn from the study, and another patient withdrew himself from the study.

Regarding the drug's ability to stabilize early total cholesterol levels, the most promising doses appeared to be 1.2, 1.4, or 1.6 g/kg, although it is difficult to make any conclusion from this quantity of data. Not surprisingly, triglyceride and LDL-C levels seemed to be more responsive to lipid emulsion therapy at all doses compared with HDL-C levels, which remained at lower levels overall. All patients had pro-inflammatory HDL represented by the HII ratio > 1, consistent with our prior work.[13,39] Because of the limited amount of PON-1 and HII data, it is difficult to make any assessment about the influence of individual drug dosages on HDL antioxidant function. More in-depth determination will be made in the phase II trial that is underway.

To our knowledge, this is the first study to attempt to stabilize cholesterol levels in patients with sepsis or septic shock. Other studies have employed fish oil–containing lipid emulsions for varying reasons in similar populations, but not with the direct intent of improving lipid profiles. The lipid infusion and patient outcomes in sepsis (LIPOS) clinical trial by Dellinger et al.[46] used a phospholipid emulsion (GR270773) in presumed gram-negative sepsis patients with the idea of binding and clearing endotoxin. The trial had negative results overall, but a later secondary analysis found that in patients with adequate liver function and total cholesterol levels >40 mg/dL or HDL-C levels >20 mg/dL that treatment with GR270773 reduced mortality significantly.[47] Although an obvious weakness of the latter study is that it was a secondary analysis, it does at least conceptually support the hypothesis of a need for some amount of cholesterol substrate to bind and clear bacterial toxins. The idea of augmenting bacterial toxin clearance via the lipid pathway was also recently mentioned as a top 10 area for future research in the Intensive Care Medicine sepsis research agenda.[48]

Another randomized controlled trial of 60 ICU sepsis patients demonstrated clinical efficacy for improving organ failure and mortality (prespecified subset of patients) after administration of a pure fish oil emulsion.[24] In a single-center placebo controlled trial of sepsis

patients comparing pure fish oil emulsion to a medium and long-chain triglyceride, significant reductions in inflammatory cytokines in the fish oil group were demonstrated.[49] Finally, a large study of 661 critically ill patients receiving total parenteral nutrition, of whom 292 had sepsis, fish oil doses of 0.1 to 0.2 g/kg/d showed significant reductions in ICU length of stay and hospital length of stay, and mortality was significantly reduced in the cohort of patients with abdominal sepsis (n = 276) receiving standard total parenteral nutrition.[50]

The major limitation of this study was a small sample size of 8 patients completing the study protocol. However, this phase I trial was designed to test the safety and tolerability of the lipid emulsion and not efficacy. We consider that despite the small number of patients and given a critically ill patient cohort (median SOFA of 8), the demonstrated safety of lipid emulsion therapy in early sepsis provides support for proceeding with a phase II trial.

5 | CONCLUSION

This phase I trial demonstrates the safety and tolerability of fish oil–containing lipid injectable emulsion in early sepsis as an adjunctive treatment. A currently underway phase II pilot study will test clinical efficacy for cholesterol stabilization in sepsis.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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