

**Comparison of Soybean-based Oil and MCT-olive-fish-soy Oil Intravenous Lipid Emulsions on Soluble Adhesion Markers in Preterm Neonates with Sepsis: A Randomized Controlled Trial**

**Running Title:** IV LIPID EMULSIONS IN PRETERM INFANTS WITH SEPSIS

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**Received:** October 26, 2018; **Initial review:** April 15, 2019; **Accepted:** August 1, 2019.

**PII:** S097475591600134

***Note:** This early-online version of the article is an unedited manuscript that has been accepted for publication. It has been posted to the website for making it available to readers, ahead of its publication in print. This version will undergo copy-editing, typesetting, and proofreading, before final publication; and the text may undergo minor changes in the final version.*

**ABSTRACT**

**Objectives:** To compare the effects of two different intravenous lipid emulsions on soluble adhesion markers in preterm infants with sepsis. **Methods:** This randomized controlled pilot trial was conducted between February 2016 to February 2017. 40 preterm infants with sepsis were enrolled and assigned to receive either Medium chain triglyceride-Olive-Fish-Soy lipid emulsion (MOFS-LE) or soybean oil-based lipid emulsion (S-LE). Outcomes of the study were changes in sICAM-1 and leukocyte integrin  $\beta$ 2 levels, and growth after 7 days of intervention. **Results:** Leukocyte integrin  $\beta$ 2 was significantly higher in MOFS-LE group. No statistically significant differences were observed for sICAM-1, duration of mechanical ventilation and antibiotics treatment, and mortality rate. **Conclusions:** Leukocyte integrin  $\beta$ 2 was significantly higher in preterm septic neonates who received MOFS-LE.

**Keywords:** *Parenteral nutrition, Polyunsaturated fatty acids, Soluble adhesion molecules*

**Trial registration:** ClinicalTrials.gov (NCT03275090)

Preterm infants with sepsis are more vulnerable to undernutrition [1]. Adequate parenteral nutrition (PN) minimizes weight loss, mortality and improves neurodevelopment [2]. Lipid emulsions (LEs) are important components of PN providing energy, essential fatty acids and vitamins [3].

Pure soybean oil-based lipid emulsions (S-LE) have been used commercially worldwide, and consist of long-chain fatty acids with omega 3 to omega 6 ratio of 1:5.5 [4]. These fatty acids play important role in several physiological processes such as immune and inflammatory response, platelet functions and early neural and visual development [5]. However, there are several studies suggesting that S-LE could have hazards due to excess linoleic acid and polyunsaturated fatty acid [6]. MOFS (MCT-olive-fish-soy oil) lipid emulsions (MOFS-LE) are mixtures of 30% medium chain triglycerides (MCT), 25% olive oil, 15% fish oil, and 30% soybean oil, and are supposed to have better immunomodulatory and anti-inflammatory properties [3].

There are several studies comparing efficacy and safety of S-LE and MOFS-LE in neonates but there is no consensus on the ideal LE [3]. The present study was designed to compare short-term effects of S-LE and MOFS-LE on soluble adhesion markers of sepsis and growth in preterm infants.

**METHODS**

This randomized controlled double-blind pilot trial was conducted in a university-affiliated neonatal care unit (NCU) of Mansoura (Egypt) from February 2016 to February 2017. The study was approved by Medical Research Ethical Committee of Medical Faculty of Mansoura University.

Preterm neonates with possible sepsis who had positive isolates on blood culture were considered eligible for inclusion. Neonates with major congenital malformations, inborn errors of

metabolism, hypoxic-ischemic encephalopathy and congenital infections were excluded. Neonates were enrolled after obtaining written informed consent from their legal guardians.

A fixed block randomization (4 per block) was used to generate the sequence. Opaque sealed envelopes were used for allocation concealment. The study medications were dispensed in identical appearing coded bottles from the outpatient department pharmacy. Participants and care providers were all blinded to the intervention. The randomization sequence and the key to the code on the medication bottles were kept with a researcher who was not involved in patient enrolment, medication administration or measuring outcome. Patients were randomized to receive parenteral nutrition containing MOFS-LE or S-LE (Smoflipid, 20% Intralipid respectively, Fresenius Kabi, Uppsala, Sweden) for 7 days. PN was prepared aseptically by a special NCU nurse. The initial dose of LE was 0.5 g/kg/day on first day of PN, increased to a maximum of 3.5 g/kg/day. When serum triglyceride level exceeded 250 mg/dL, the lipid dosage was reduced by 25%. Amino acids, carbohydrates, trace elements, vitamins and electrolytes were prescribed in both groups. Neonates with early-onset sepsis received ampicillin and gentamicin while those with late-onset sepsis received flucloxacillin with either cefotaxime or gentamicin.

In all neonates, descriptive clinical data were collected at enrollment and growth data till 7 days post-randomization. Laboratory workup included complete blood count (CBC), CRP, blood culture using BACTEC 9120 culture system, serum creatinine, serum triglyceride, and blood glucose. Soluble intercellular adhesion molecule 1 (sICAM-1) and leukocyte integrin  $\beta 2$  were measured by ELISA.

Primary outcomes were changes in levels of sICAM-1 and leukocyte integrin  $\beta 2$  after seven days of receiving the lipid emulsions. Secondary outcomes included changes in growth parameters (weight, length and head circumference), duration of mechanical ventilation and antibiotics treatment, and mortality. A convenience sample of 40 neonates was planned for this study.

*Statistical analysis:* Chi-square and Fisher exact tests were used for categorical variables. Between-groups comparisons were done using Mann–Whitney and Student's t-tests. Within-group comparisons were done by Wilcoxon and paired t-tests. An intention to treat analysis was done. SPSS version 22 was used for statistical analyses.

## RESULTS

Ninety preterm infants were assessed for eligibility; 50 were excluded and 40 infants with sepsis were included (**Fig. 1**). Both groups were comparable for baseline characteristics (**Table I**). They were also comparable for the hematological parameters and CRP. Klebsiella was the commonest organism followed by *Staphylococcus aureus* and *E. coli* ( $n=12$ , 2 and 2, respectively in MOFS-LE group; and  $n=9$ , 7 and 2, respectively in S-LE group). Group B streptococcus and candida were isolated in two patients each in MOFS-LE group; and pseudomonas was isolated in two patients of S-LE group.

**Table II** compares the outcomes of the study between the two groups. sICAM1 and leukocyte integrin  $\beta 2$  were significantly higher in MOFS-LE group on 7<sup>th</sup> day. Within-group comparison showed that sICAM-1 increased significantly in both groups from 1<sup>st</sup> to 7<sup>th</sup> day ( $P=0.030$  in S-LE group and  $P=0.001$  in MOFS-LE group) while leukocyte integrin  $\beta 2$  increased significantly in MOFS-LE group only ( $P=0.001$ ). For the growth outcomes, within-group comparison revealed significant body weight increase in both groups ( $P=0.010$  in S-LE group and  $P=0.005$  in MOFS-LE group). Length increased significantly in MOFS-LE group ( $P=0.004$ ). No significant differences were observed between both groups as regards mortality, duration of mechanical ventilation or antibiotics treatment.

## DISCUSSION

In the present study there was no evidence of any significant effect of the intervention in the levels of sICAM-1, while leukocyte integrin  $\beta 2$  was significantly higher in the MOFS-LE group. There was no evidence of any significant effect of the intervention on the growth parameters of weight, length and head circumference between both groups.

Several soluble adhesion molecules are released in sepsis. Among these, sICAM-1 and leukocyte integrin  $\beta 2$  are early predictors with high specificity and sensitivity, but are important in controlling the infective process [7]. In the present study the increased level of sICAM-1 in both groups is similar to that observed by Edgar, *et al.* [8]. Briassoulis, *et al.* [9] reported that septic infants with the highest sICAM-1 levels had better outcomes. The significantly higher levels of leukocyte integrin  $\beta 2$  in the MOFS-LE group were similar to the findings of Wanten, *et al.* [10] who reported that LEs containing MCT were associated with a higher expression of leukocyte integrin  $\beta 2$ .

Body weight did not differ significantly between groups while it increased in both groups similarly before and after intervention. This observation is similar to that noted by Uthaya, *et al.* [11]. However, others have reported better weight gain with S-LE [3]. Length increments were not significantly different but was expected to be better with MOFS-LE due to fish oil component of MOFS-LE, being rich in docosahexaenoic acid [12].

The limitations of the study are that it was a single-center study with a small sample size. Moreover, the evaluation was done for a very short time period.

We conclude that MOFS lipid emulsions may result in higher levels of soluble adhesion molecules, which could potentially impact outcome in preterm septic neonates. Larger adequately powered studies would be needed to study the clinical and functional significance of these effects.

*Contributors:* MA: acquisition of clinical data, drafting the manuscript. YW: analysis and interpretation of data, revising the article draft critically for important intellectual content. BS: conception and design of the study, analysis and interpretation of the clinical data, and drafting the article. AM: acquisition of laboratory data, analysis and interpretation of the clinical data, and drafting the article. All author approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the

work are appropriately investigated and resolved.

*Funding:* None; *Competing Interest:* None stated.

**Acknowledgement:** Nursing staff of neonatal care unit of Mansoura University Children's Hospital, Egypt for their help and co-operation.

#### WHAT THIS STUDY ADD?

- Higher levels of soluble adhesion molecule leukocyte integrin  $\beta_2$  are found in preterm infants receiving Medium Chain triglyceride-Olive-Fish-Soy (MOFS)-based lipid emulsion in comparison to those receiving soybean-based lipid emulsion.

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**TABLE I** BASELINE CHARACTERISTICS OF STUDY GROUPS

<i>Characters</i>	<i>S-LE group (n=20)</i>	<i>MOFS-LE group (n=20)</i>
Gestational age (wks)*	31.7 (2.0)	31.6 (1.5)
Male sex	14 (70)	8 (40)
<i>Growth status</i>		
AGA	13 (65)	16 (80)
SGA	6 (30)	4 (20)
LGA	1 (5)	0
<i>Onset of sepsis</i>		
Early onset	12 (60)	8 (40)
Late onset	8 (40)	12 (60)
Maternal age (y)*	27.3 (5)	27 (5.4)
Cesarean delivery	18 (90)	15 (75)
<i>Risk factors for sepsis</i>		
PROM	13 (65)	18 (90)
Maternal UTI	10 (50)	7 (35)
Maternal fever	7 (35)	7 (35)
Chorioamnionitis	4 (20)	5 (25)
Central line insertion	7 (35)	3 (15)
Surgery	0	2 (10)

Data are shown as number (%), except \* mean (SD); AGA: Appropriate for gestational age; SGA: Small for gestational age; LGA: Large for gestational age; PROM: Prolonged rupture of membranes; UTI: Urinary tract infection; S-LE: soybean oil-based lipid emulsion; MOFS-LE: Medium chain triglyceride-Olive-Fish-Soy lipid emulsion

**TABLE II** OUTCOME VARIABLES BETWEEN THE GROUPS

<i>Parameters</i>	<i>S-LE group (n=20)</i>	<i>MOFS-LE group (n=20)</i>	<i>P value</i>
sICAM-1 (pg/ml) <sup>#</sup>			
Day 1	1214 (951.2-1658.5)	1661.5 (819.4-2225.5)	0.02
Day 7	1493 (806.6-2018.7)	2354 (1517.6-2902.1)	0.02
Leukocyte integrin $\beta$ 2 (pg/ml) <sup>#</sup>			
Day 1	19.5 (15.3-24.5)	20 (14.3-24.4)	0.41
Day 7	20.3 (15.2-25.6)	25 (22.8-29.7)	0.02
Weight (Kg) <sup>#</sup>			
Day 1	1.35 (0.8-1.9)	1.4 (0.7-1.6)	0.89
Day 7	1.4 (1.1-2.9)	1.5 (1.0-1.8)	0.92
Length (cm) <sup>*</sup>			
Day 1	40.3 (4)	39.1 (3.2)	0.30
Day 7	40.4 (4.1)	39.4 (3.1)	0.43
Head circumference (cm) <sup>*</sup>			
Day 1	29.1 (3.6)	29.2 (3.4)	0.90
Day 7	29.6 (3.4)	29.9 (3.9)	0.67

*sICAM-1: Soluble intercellular adhesion molecule 1; Data are shown as \*mean (SD) or #median (IQR);*

*S-LE: soybean oil-based lipid emulsion; MOFS-LE: Medium chain triglyceride-Olive-Fish-Soy lipid emulsion*



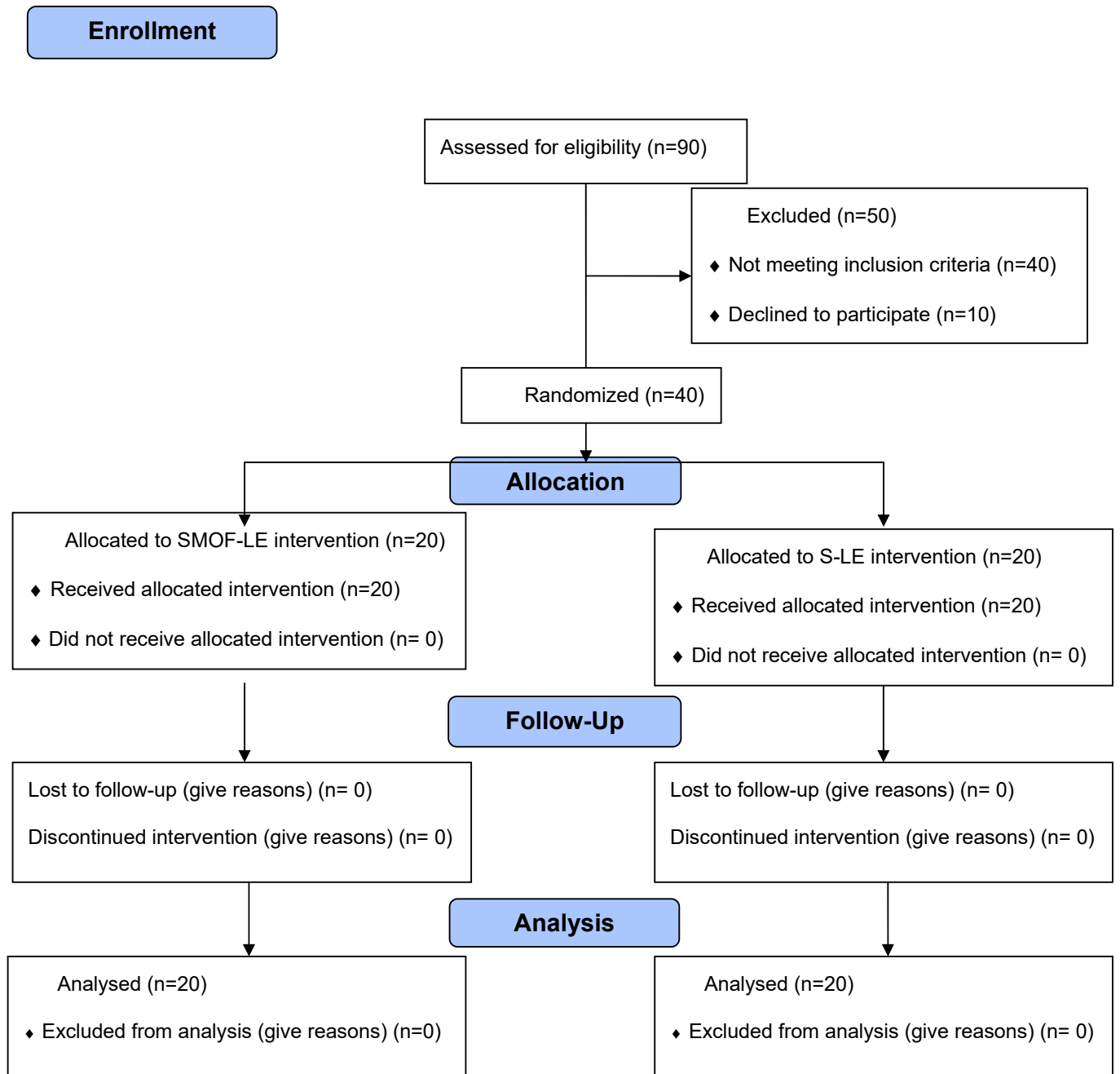


FIG. 1. Consort flow diagram of the trial.