Parenteral nutrition with fish oil supplements is safe and seems to be effective in severe preterm neonates with respiratory distress syndrome

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Parenteral nutrition with fish oil supplementation in premature neonates with severe respiratory distress syndrome. A preliminary study

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In the early stage of life, premature neonates are fed with a parenteral nutrition solution (1). For years, lipid emulsion based on soybean oil have been used in neonatal intensive care unit (NICU). Soybean oil is rich in n-6 polyunsaturated fatty acids (PUFAs) and has a relatively low antioxidant and anti-inflammatory content. Prematurity is often associated with severe respiratory distress syndrome, which is caused by a lack of surfactant together with the combined effects of mechanical ventilation and oxygen therapy. In this context of ventilation-induced lung injury and oxygen toxicity, premature neonates with severe respiratory distress syndrome have a high risk of developing bronchopulmonary dysplasia (BPD). BPD is defined in 3 grades: mild when supplemental oxygen is needed for 28 days but room air at 36 weeks corrected gestational age or at discharge, moderate when supplemental oxygen is required for 28 days and $FiO2 < 0.30$ at 36 weeks corrected gestational age or at discharge, and severe when supplemental oxygen is needed for 28 days and $FiO2 > 0.30$ or positive pressure support at 36

weeks corrected gestational age or at discharge (2). Some studies have stated that BPD is considered as an inflammatory disease (3;4). Animal study (5) and clinical observation (6) have shown that n-3 long-chain PUFAs (LCPUFAs ; e.g., eicosapentaenoic acid (EPA: 20:5n-3) and docosahexaenoic acid (DHA: 22:6n-3)) decrease pulmonary inflammation. In this context, some neonatologists (7-9) have used parenteral nutrition solution supplemented by pharmaceutical fish oil to improve the lung fatty acid profile and improve immune function in preterm neonates (10).

Pharmaceutical fish oil supplementation can be achieved using the commercially available SMOFlipid® emulsion which is approved for preterm infant nutrition (Fresenius Kabi, Sèvres, France). Studies have shown that SMOFlipid® emulsion was safe and well tolerated in more than 150 preterm neonates, including those in three clinical trials (7-9). However, any benefits of SMOFlipid® emulsion noted in clinical trial are not specific to the beneficial effects of n-3 LCPUFAs because SMOFlipid® contains n-3 LCPUFAs as well as medium-chain triglycerides and n-6 LCPUFAs, which have different physiological effects (11). Omegaven® is a pure n-3 LCPUFA lipid emulsion. Here, we present a preliminary study of using Omegaven® as a new fish LCPUFAs rich lipid emulsion for use in the treatment of preterm neonate with respiratory distress syndrome.

For this study and according to Declaration of Helsinki, written informed consent was obtained from both parents of the preterm neonate, and the study was approved by the Ethical Committee of Lille (Comité de Protection des Personnes Nord-Ouest IV dans la Recherche Biomédicale de Lille N° 04/70) and the French competent authority (AFSSAPS). This study included 12 preterm neonates

(median gestational age of 30 weeks [27–32]) with severe respiratory distress syndrome, which was defined as a fraction of inspired oxygen of 0.35 (oxygen saturation measured by pulse oxymetry between 90% and 95%) at 36 h of age together with the need for mechanical ventilation (median duration: 5 days [3–26]) according to the classification of Couchard et al (12). All premature neonates with severe respiratory distress received artificial surfactant (proactant alpha) within the first hours of life.

Before randomization, all preterm neonates were continuously fed with parenteral nutrition solution and a minimal continuous enteral feeding using pooled breast milk from our local lactarium. According to the European Society for Parenteral and Enteral Nutrition and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition consensus, the target of parenteral nutrition solution was 2 *g/kg/d* for lipids (started at birth at 0.5 *g/kg/d* and gradually increased to reach 2 *g/kg/d*), 18 *g/kg/d* for glucose (started at birth at 8 *g/kg/d* and gradually increased by steps of 2 *g/kg* to reach 18 *g/kg/d*) and 4 *g/kg/d* for proteins. This target was not modified with advancement of enteral feeding. Parenteral nutrition solution with fish oil supplementation (Omegaven® 10%) or control oil (Intralipid® 10%) was started at 42–54 h of life and was continued until 12–13 days of life. Randomization was performed using sealed envelopes centralized in the NCIU. Randomization was equilibrated by block size of 6, according to a ratio of intervention to control subjects of 2:1 (4 intervention/2 control). Double blinding of the identity of the commercial lipid emulsions: Omegaven® 10% *vs* Intralipid® 10% was assured by specific stickers that masked the labeling information and included the subject's randomized number

(and Good Clinical Practice quality assurance information specifically requested for Clinical Trial).

The blinded lipid emulsions tested were diluted at ratio 1/10 in a syringe (for infusion pump) in sterile condition at the NCIU unit : 50 ml of lipid emulsion was prepared daily by mixing 5 ml of blinded Omegaven® 10% or 5 ml of blinded Intralipids® 10% with 45 ml of Intralipid® 20%. This procedure achieved a final lipid composition of 18 % in each groups.

Both at baseline and at 28 days of age, the preterm neonate' weight did not differ between groups (Table 1). Clinical outcomes at the baseline and at 28 days of age are shown in Table 1. Some sepsis (by Gram-negative bacteria species) occurred early (1/8 in interventional group and ¾ in control group) and only one in each group were until present at 28 days of life (Table 1). The blood clinical parameters are presented in Table 2. These parameters did not differ between the two groups at the baseline and at the end point of 28 days except for platelet count, which was lower at 28 days of life in the control group than in the n-3 LCPUFA group. No adverse drug reactions, adverse events of special interest, or serious adverse events were observed during the 28-day study period. We observed a significantly shorter oxygen therapy duration in the n-3 LCPUFA group compared with the control group: 33 days [12–100] *vs* 254 days [42–593], respectively ($p = 0.048$, Mann–Whitney *U* test).

Minimizing lung injury in preterm neonates with severe respiratory distress syndrome is one of the main concerns in the NICU, and nutritional intervention is a promising method to achieve this (13). This study reports for the first time the use of Omegaven® as a new source of n-3 LCPUFAs for parenteral nutrition solution with fish oil supplementation in preterm neonates with severe respiratory

distress syndrome. The strong anti-inflammatory effect of EPA and DHA, which has been demonstrated in both animal models (5) and human conditions such as asthma, chronic obstructive pulmonary disease, and cystic fibrosis, may decrease the risk of developing BPD (14;15). Our study shows that Omegaven® could be used as a source of n-3 LCPUFAs for parenteral nutrition solution with fish oil supplementation in preterm neonates with severe respiratory distress syndrome. The greater oxygen therapy duration observed in the control group could be due to the presence of sepsis at baseline of a potential effect of n-3 LCPUFAs in interventional group. In this context, effects of n-3 LCPUFAs on oxygen therapy duration should be tested in a blinded randomized clinical trial.

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Table 1: Weight and clinical outcome at baseline and at 28 days of age

	n-3 LCPUFAs group **n = 8**		Control group **n = 4**	
	baseline	*28 days*	*baseline*	*28 days*
Weight (Kg)	1.45 [0.93- 1.83]	1.70 [1.07–2.47]	1.51 [0.93–1.80]	2.24 [1.15–2.32]
Late onset sepsis	0	1	0	1
Pulmonary hypertension*	4	0	3	0
Necrotizing enterocolitis	0	0	0	1

*Diagnosis of pulmonary hypertension was established with the presence of a right and left bidirectional shunting across the ductus arteriosus detected by echocardiographic assessment.

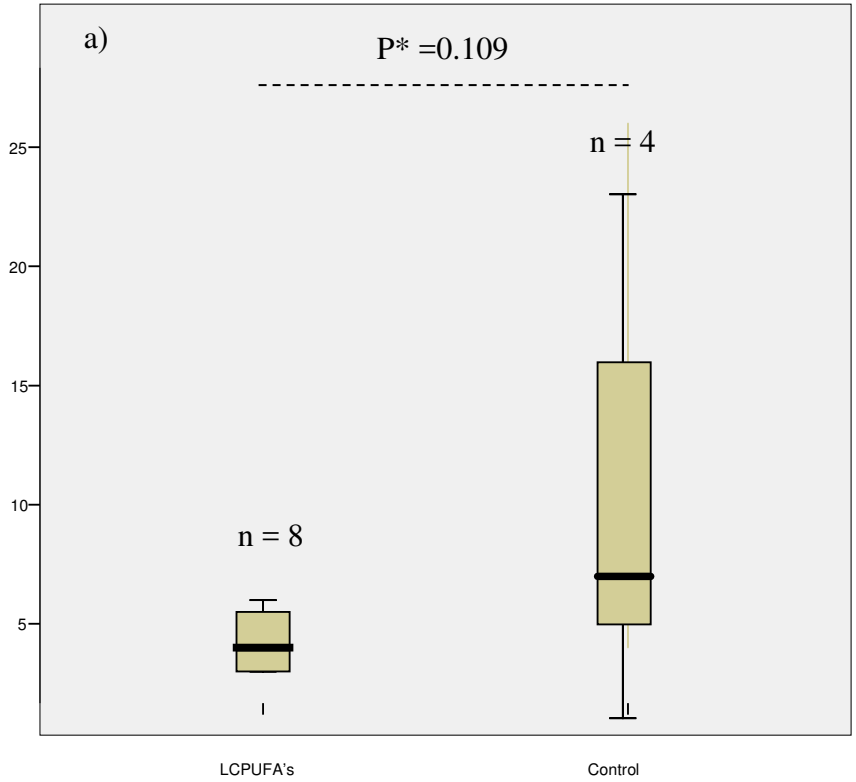
Table 2: Blood biological parameters at baseline and at 28 days of age

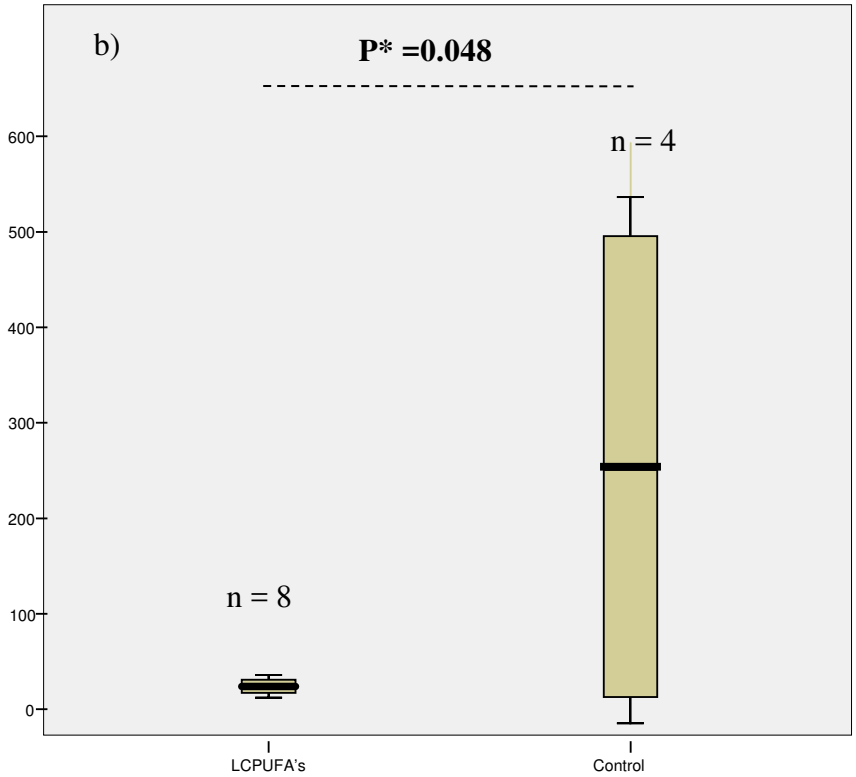
Median (ranges)	n-3 LCPUFAs group **n = 8**		Control Group **n = 4**		p[1]	p[2]
	baseline	*28 days*	*baseline*	*28 days*		
Haemoglobin (*g/L*)	135.0 [85.1-165.7]	110.2 [76.0-128.2]	130.2 [112.5-149.3]	113.8 [100.0-128.7]	0.4	0.7
Haematrocrit (*%*)	32.4 [10.0-44.5]	32.9 [21.6-38.7]	37.8 [32.4-45.7]	33.6 [31.0-38.3]	0.6	0.4
RBCs (*10^{12} counts/L*)	3.6 [2.2-4.2]	3.3 [2.4-4.9]	3.4 [2.7-4.6]	4.0 [3.5-4.9]	0.8	0.9
WBCs (*10^{9} counts/L*)	12.1 [7.4-20.8]	13.8 [6.3-20.4]	10.0 [9.6-14.2]	16.6 [13.2-20.4]	0.9	0.8
Platelets (*10^{9}counts/L*)	185 [67-228]	299 [236-332]	146 [110-170]	167 [151-270]	0.9	**0.01**
Triglycérides (*mmol/L*)	0.9 [0.6-1.0]	0.8 [0.4-1.2]	0.7 [0.5-0.9]	0.8 [0.7-0.9]	0.9	0.8
Créatinine (*µmol/L*)	32.0 [17.7-78.0]	47.4 [39.0-55.8]	76.6 [45.8-85.0]	42.8 [38.0-49.2]	0.9	0.4
Total bilirubin (*µmol/L*)	228 [125-392]	65 [45-92]	180 [117-339]	69 [38-92]	0.7	0.6
C-reactive protein (*mg/dL*)	7.7 [0.1-48]	0.1 [0.1-23]	3.1 [0.1-6.0]	3.6 [0.1-6]	0.2	0.4

[1] U-Mann-Whitney test between LCPUFAs group and control group at baseline
[2] U-Mann-Whitney test between LCPUFAs group and control group at 28 days of age
RBGs = Red Blood Cells
WBCs = White Blood Cells

n= 4

Figure 1: Box plot of duration of continuous mechanical ventilation (a) and oxygen therapy duration (b) at 28 days of age in the 2 groups





* U-Mann Whitney