Original Article

Parenteral Fish-Oil Lipid Emulsions in Retinopathy of Prematurity: A Retrospective Comparative Study

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Abstract

Purpose: To evaluate the effects of a fish oil-containing regimen on the severity of retinopathy of prematurity (ROP) in preterm infants.

Methods: In this retrospective, observational study, 82 preterm infants with documented retinal examinations were evaluated. Patients' demographic data, associated morbidities, the worst ROP zone, stage, and the presence of plus disease during the follow-up examinations, and the need for ROP treatment in the two groups were recorded and analyzed.

Results: Forty-three infants were treated with INTRAlipid®, and 39 infants were treated with 20% SMOFlipid. There were no differences in gestational age, birth weight, and associated morbidities between the two groups. No differences were observed among the two groups in their need for treatment ($P = 0.51$), ROP zones ($P = 0.62$), and plus disease ($P = 0.38$). Although no difference was seen in ROP stages between the groups ($P = 0.41$), in subgroup analysis, Stage 3 (severe ROP) occurred significantly lower in the SMOFlipid group ($P = 0.04$) and Stage 0 occurred significantly higher in the SMOFlipid-treated infants ($P = 0.05$).

Conclusions: This study showed no difference between the two groups regarding the need for the treatment. The lower prevalence of severe ROP in preterm infants receiving SMOFlipid emulsion was observed comparing to the INTRAlipid-treated infants.

Keywords: Docosahexaenoic acid, INTRAlipid, Preterm, Retina, Retinopathy of prematurity, SMOFlipid

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Submitted: 26-Apr-2019; **Revised:** 01-Jul-2019 ; **Accepted:** 25-Jul-2019; **Published:** 23-Mar-2020

Introduction

Retinopathy of prematurity (ROP) is one of the leading causes of visual morbidity worldwide.[1] Although the incidence has declined in developed countries, the prevalence remains high in developing areas due to the improved survival of extremely premature infants and lack of proper ROP screening programs. ROP develops in 38% of infants with gestational age (GA) <32 weeks.[1] It could be a self-limited disease with full peripheral vascularization and without any complications or a devastating disease with retinal detachment and poor visual prognosis. The prognosis mainly depends on early diagnosis, severity of the disease, and prompt treatment in required cases.

The main events in the pathophysiology of ROP include initial phase of oxygen-induced vascular obliteration and the subsequent period of hypoxia-induced vessel proliferation.[2] Low GA and low-birth weight (BW) are the two main established risk factors in ROP.[2] Furthermore, there may be other possible risk factors as retinal differentiation and maturation, and structural stability are disrupted in preterm birth. Docosahexaenoic acid (DHA) is an omega-3 fatty acid

Access this article online

Quick Response Code:

Website: www.jcurrophthalmol.org

DOI: 10.4103/JOCO.JOCO_23_20

How to cite this article: Gharehbaghi G, Mohagheghi P, Sedaghat A, Riazi-Esfahani H, Mirghorbani M, Khosravi N. Parenteral fish-oil lipid emulsions in retinopathy of prematurity: A retrospective comparative study. J Curr Ophthalmol 2020;32:69-74.

which is synthesized from α-linolenic acid (ALA). Fish-oil lipid emulsions contain omega-3 fatty acids such as DHA.[3] This fatty acid is required for brain growth and neurodevelopment.[4] It was shown that 20% of the total fatty acid contents of the infant retina is composed of DHA.[5] Although preterm infants are capable of converting ALA to DHA, it is not clear whether this *de novo* pathway is sufficient for their needs or not.[6-8] Furthermore, preterm infants already lack third-trimester lipid store as DHA accumulation mainly occurs between 26 and 40 weeks. Hence, their daily DHA requirements would be higher.[9] Some studies evaluated the preventive value of parenteral fish-oil lipid emulsions in ROP. [10-19] Their main outcomes were the need for laser treatment and ROP severity. Although the treatment of ROP is dramatically changed in many referral clinics with the evolution of anti-vascular endothelial growth factor (anti-VEGF) agents such as intravitreal injection of bevacizumab (IVB), the criteria for the treatment remains unchanged.

We aimed to evaluate the effect of replacement of soybean oil emulsion with recent regimens containing fish-oil emulsion on ROP severity regarding different zones and stages and the need for treatment whether IVB or laser therapy in a retrospective, observational study.

Methods

The Institutional Review Board/Ethics Committee of the Iran University of Medical Sciences approved this retrospective, observational study. The medical records of preterm infants with BW <2000 g and GA <34 weeks who were admitted to the Neonatal Intensive Care Unit (NICU) of Rasoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran, were collected. Only records with documented fundoscopy examination with the following inclusion criteria were included: at least 16 weeks of follow-up after the first fundus examination, absence of Stage 4b or 5 ROP before treatment, and no concomitant ocular diseases (such as congenital cataract or glaucoma). Infants were treated with total parenteral nutrition (TPN) with lipid emulsions from the 3rd day of life as a continuous infusion for 24 h/day. The time periods were defined as April 1, 2011–September 30, 2013 and January 30, 2015–March 30, 2017. The reason was that in 2011–2013, preterm infants received soybean oil emulsion (Intralipid® 20% [Fresenius Kabi AB, Uppsala, Sweden]: soybean oil 200 g/dL, egg phospholipids 12 g/dL, glycerol 22.5 g/dL, and Vitamin E 57 mg α-TE/L) while after 2014, the treatment regimen was changed in many pediatric centers to fish-oil emulsion (SMOFlipid20%® [Fresenius Kabi AB, Uppsala, Sweden]: soybean oil 60 g/dL, MCT 60 g/dL, olive oil 50 g/dL, fish oil 30 g/dL, egg phospholipids 12 g/dL, glycerol 25 g/dL, and Vitamin E 200 mg α-TE/L), as it was shown that preterm neonates who underwent SMOFlipid regimen had increased DHA and Vitamin E concentrations and decreased markers of oxidative stress and arachidonic acid compared to neonates who underwent INTRAlipid regimen.[20,21] The parenteral nutrition was administered with an initial daily dose of 0.5 g of lipids/kg, which was increased by 0.5 g of lipids/kg body weight every 24 h to a maximum of 3.0 g of lipids/kg/day. Trace elements, lipid-soluble vitamins, and water were also administered as standard TPN protocol. Considering enteral feeding, all infants were fed initially with breast milk and advanced at 20 ml/kg/day as tolerated. In cases of formula milk, infants were fed with Aptamil Formula (Milupa, Friedrichsdorf, Germany) enriched with Omega-3 with about 4.4 g lipids/100 ml. Intravenous lipid infusion was replaced progressively with enteral intake according to feeding tolerance to maintain total lipid dose of 3.0–3.5 g of lipids/kg/day. The same nutritional protocol was administered in both groups.

Medical records were studied, and the related data were collected, including GA, BW, APGAR 1 min score, supplement type, and sex. Preterm infants had been screened for ROP with indirect ophthalmoscopy at 4–6 weeks chronological age or 31–33 weeks postmenstrual age (whichever was later), and follow-up examinations had been continued at least until the near-complete vascularization was achieved. The worst ROP zone, stage, and the presence of plus disease during the follow-up examinations, need for treatment for ROP (whether laser or IVB), mean age at treatment, and duration of follow-up period were recorded. The associated disorders such as sepsis, intraventricular hemorrhage, oxygen therapy, duration of mechanical ventilation (intubation), the number of red blood cell transfusion, and phototherapy were also documented. Infants with the following criteria were excluded: incomplete registration, major congenital malformation, inborn metabolic errors, symptoms of congenital infection, and the history of surgery for retinal detachment.

ROP screening and treatment were done by one experienced pediatric vitreoretinal surgeon. In cases of threshold and prethreshold disease, the treatment was done within 48 h whether with IVB injection or laser therapy. Otherwise, serial follow-up was done until full vascularization of the retina was observed (as it is necessary in cases of IVB). The primary outcome was the need to treat whether with laser or IVB injection, and the secondary outcomes were the ROP stage, zone, and the existence of plus disease.

Statistical analysis

To evaluate the patient-specific parameters between the groups, we used the *t*-test, Mann–Whitney U-test, Chi-square test, and Fisher's exact test as appropriate. To assess the eye parameters when considering the correlation between two eyes in a single patient, the generalized estimating equation (GEE) was used. $P \leq 0.05$ was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics for Windows software version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Three hundred and forty-one infants were enrolled in this study. One hundred and eighty-seven infants received INTRAlipid

regimen, and 154 infants received SMOFlipid. Forty patients in the INTRAlipid group (22%) and 39 patients in the SMOFlipid group (25%) had documented retinal examination (at least Stage 0). Demographic data and associated morbidities are shown in Tables 1 and 2. Nearly 41.9% (18/43) of patients in the INTRAlipid group and 59% (23/39) of patients in the SMOFlipid group were girls ($P = 0.12$). The mean GA was 28.3 ± 2.2 and 27.9 ± 2.0 in the INTRAlipid and SMOFlipid groups, respectively ($P = 0.43$). The average of total parenteral dosage was 18.1 ± 3.9 and 17.8 ± 2.8 g at day 8 ($P = 0.70$) and 40.0 ± 8.9 and 38.7 ± 6.9 g at day 15 ($P = 0.49$) in the INTRAlipid and SMOFlipid groups, respectively. The mean follow-up time after the first retinal examination was 33.3 ± 7.4 and 29.7 ± 5.7 weeks in the INTRAlipid and SMOFlipid groups, respectively.

Zone and stage subgroups in the INTRAlipid (86 eyes) and SMOFlipid (78 eyes) groups are shown in Table 3. In the SMOFlipid group, retinal vascularization in most eyes was documented in Zone 3 (53.8% in Zone 3 vs. 41.0% in Zone 2), whereas in the INTRAlipid group, retinal vascularization in most eyes was in Zone 2 (51.2% in Zone 2 vs. 45% in Zone 3). However, none of these differences were significant. Regarding different stages, although there was no significant difference between ROP stages among the two groups ($P = 0.41$), in subgroup analyses, Stage 3 occurred significantly lower in the SMOFlipid group compared to the INTRAlipid group (14% vs. 9%; $P = 0.04$). Furthermore, Stage 0 (incomplete vascularization) alone was statistically higher in the SMOFlipid group ($P = 0.05$). ROP plus was not significantly different between the two groups, although it was lower in the SMOFlipid group than in the INTRAlipid group (16.7% vs. 24.2%; $P = 0.38$). Need for the treatment with either laser or anti-VEGF was lower in the SMOFlipid group than in the INTRAlipid group, although it was not significant (15.4% vs. 20.9%; $P = 0.51$) [Table 3].

Discussion

In this study, we compared the effects of SMOFlipid and INTRAlipid emulsion infusion as part of standard TPN protocol on ROP severity and progression in infants with GA <32 weeks and BW <1500 g. The main difference between the two regimens is the presence of fish oil (30 g/dL) in 20% SMOFlipid infusion. Fish oil includes omega-3 fatty acids such as eicosapentaenoic acid and DHA. DHA was shown to be required for healthy neurodevelopment (sensory, motor, perceptive, and cognitive)[22] and immune functions.[23] Furthermore, it was shown that retinal photoreceptor cell membranes are enriched with DHA, comprising 35% of total fatty acids in rod outer segments and 20% of the total fatty acid contents of the retina.[5] Other experimental studies confirmed the significant role of DHA in retinal stability.[24,25] While induced DHA-deficient animals showed abnormalities in cognition, visual acuity, and retinal structures;[24] improved visual outcomes were seen in infants fed with DHA-containing formula compared with infants that were fed no DHA.[26] Hence, the concept that a DHA-containing parenteral regimen shows some effects on the improvement of retinal prematurity has been evaluated in some studies [Table 4]. The evidence provided by each study was rated according to the British Centre for Evidence-Based Medicine guidelines.[27]

Pawlik *et al*. in a series of studies (Level I and II) described the protective effects of Omegaven therapy (fish oil-containing lipid) on the prevention of severe ROP.[14-16] Furthermore, two meta-analyses conducted by Kapoor *et al*.[12] and Vayalthrikkovil *et al*.[18] both reported protective effects of fish-oil-containing lipid emulsions on the prevention of severe ROP. However, there are some Level I studies that reported no difference between the treatment groups in any ROP or severe ROP development. Beken *et al*.,[10] Vlaardingerbroek *et al*.,[19] and Najm *et al*.[13] reported randomized clinical trials with no significant difference between an SMOFlipid regimen and a Clinoleic (80% olive oil and 20% soybean) regimen. Although there were minor differences in dosages between conducted studies (initial dosage and daily increasing dosage), the TPN protocol and lipid infusion regimens were similar and did not explain the differences in results. Although in many referral centers, SMOFlipid regimen is used as a part of TPN protocol, the reason is mainly because of improved growth rate and reduced cholestasis.[19,21]

In our study, there were no significant differences in demographic data and associated morbidities [Tables 1 and 2]. Furthermore, there was no significant difference in the average of total parenteral dosage between the INTRAlipid and SMOFlipid groups in the 1st and the 2nd weeks of life. No significant difference was detected between ROP zones considering subgroup (each zone separately) or group (all zones) analysis. Furthermore, there was no significant difference between ROP stages in group analysis ($P = 0.41$). In subgroup analyses, the lower prevalence of ROP Stage

Table 1: Demographic data of infants enrolled in the study

	INTRAlipid group				SMOFlipid group				*P*†
	Mean±SD	Median	Minimum	Maximum	Mean±SD	Median	Minimum	Maximum	
GA	28.3±2.2	28.50	23.00	33.00	27.9±2.0	28.00	24.00	33.00	0.43
BW	1128±336	1080	600	2000	1031±207	1000	550	1500	0.12
APGAR 1 min score	6±1.5	5	5	8	6±1.5	6	5	8	0.91
Parenteral lipid regimen duration	14±6	12	10	28	14±8	11	9	22	0.35
Intubation duration	10±7	7	0	47	9±7	7	0	30	0.17

†Mann-Whitney U. GA: Gestational age, BW: Birth weight, SD: Standard deviation

Table 2: Associated morbidities of infants enrolled in the study

	Count (column %)			*P*
	Total	INTRAlipid	SMOFlipid	
O_2 therapy				
No	6 (7.3)	5 (11.6)	1 (2.6)	0.20**
Yes	76 (92.7)	38 (88.4)	38 (97.4)	
Intubation				
No	64 (78.0)	36 (83.7)	28 (71.8)	0.19*
Yes	18 (22.0)	7 (16.3)	11 (28.2)	
Transfusion				
No	33 (40.2)	18 (41.9)	15 (38.5)	0.75*
Yes	49 (59.8)	25 (58.1)	24 (61.5)	
Sepsis				
No	51 (62.2)	23 (53.5)	28 (71.8)	0.08*
Yes	31 (37.8)	20 (46.5)	11 (28.2)	
IVH				
No	76 (92.7)	38 (88.4)	38 (97.4)	0.20**
Yes	6 (7.3)	5 (11.6)	1 (2.6)	
Icterus treated by phototherapy				
No	28 (34.1)	12 (27.9)	16 (41.0)	0.21**
Yes	54 (65.9)	31 (72.1)	23 (59.0)	

*Based on Chi-square test, **Based on Fisher's exact test. IVH: Intraventricular hemorrhage

Table 3: Comparing retinopathy of prematurity (ROP) zones, stages, plus disease, and the need for treatment in two groups

	Total (%)	Regimen (%)		*P*-value in subgroups	*P*
		INTRAlipid	SMOFlipid		
Need for treatment					
No	134 (81.7)	68 (79.1)	66 (84.6)		0.51§
Yes	30 (18.3)	18 (20.9)	12 (15.4)		
Plus					
No plus	130 (79.3)	65 (75.6)	65 (83.3)		0.38§
Plus	34 (20.7)	21 (24.4)	13 (16.7)		
Zone					
Zone 1	7 (4.3)	3 (3.5)	4 (5.1)	0.76§	0.62§
Zone 2	76 (46.3)	44 (51.2)	32 (41.0)	0.07§	
Zone 3	81 (49.4)	39 (45.3)	42 (53.8)	0.12§	
Stage					
Stage 0	46 (28.0)	21 (24.4)	25 (32.1)	0.05§	0.41§
Stage 1	61 (37.2)	33 (38.4)	28 (35.9)	0.12§	
Stage 2	38 (23.2)	20 (23.3)	18 (23.1)	0.23§	
Stage 3	19 (11.6)	12 (14.0)	7 (9.0)	0.04§	

§Based on GEE analysis. GEE: Generalized estimating equation

3 (which is considered severe ROP disease in most studies) was observed in the SMOFlipid group compared to the INTRAlipid group ($P = 0.04$). However, it should be noted that subgroups were small, and the difference should be considered with caution. Also, Stage 0 (incomplete vascularization) was statistically higher in the SMOFlipid group than in the INTRAlipid group ($P = 0.05$); however, this is probably not strong evidence that Stage 0 is more common in SMOF-treated infants. It could be due to freezing the disease course in the early stages or even regression of Stage 1 or 2 of the disease. In addition, observation of no difference in the need to treatment minimizes the importance of the concept.

This study was a retrospective, observational study with two different periods of time for data collection; 2011–2013 for the INTRAlipid and 2015–2017 for the SMOFlipid groups. Hence, there is the possibility of ward routine changes over time and risks of bias due to confounding factors associated with variations in care routines over time at NICU. Indeed, the study design with two different time periods for study groups was the main limitation of the study. Furthermore, the sample size was rather low ($n = 82$). The technical limitation was that the concentration of DHA in breast milk was not evaluated routinely, and hence, total intake of DHA supplemented, either enteral or parenteral, was not considered.

Table 4: Studies reporting effects of fish-oil lipid emulsion docosahexaenoic acid (DHA) infusion as part of total parenteral nutrition (TPN) protocol on retinopathy of prematurity (ROP)

Author, year	Study design, evidence level	Number of patients	Methods	Results	Significant effect
Pawlik *et al*., 2011[15]	Retrospective cohort, II	337	Treated infants with GA <30 and BW <1500 (Omegaven: 152, Clinoleic: 185) were evaluated	23 cases of severe ROP ≥ Stage 3 in control group and 9 cases in fish-oil group; relative risk of 0.48 (0.23 to 1.00)	
Pawlik *et al*., 2011[14]	Prospective observational, II	84	Treated infants with GA <30 and BW <1250 (Omegaven: 40, Clinoleic: 44) were evaluated	12 cases of severe ROP ≥ Stage 3 in control group and 3 cases in fish-oil group; relative risk of 0.26 (0.06 to 0.90)	+
Pawlik *et al*., 2014[16]	RCT, I	130	Infants with GA <30 and BW <1250 were randomized to treat with Omegaven (60) or Clinoleic (70)	22 cases of severe ROP ≥ Stage 3 in control group and 9 cases in fish-oil group; relative risk of 0.48 (0.24 to 0.96)	+
Beken *et al*., 2014[10]	RCT, I	80	Infants with GA <30 and BW <1500 were randomized to treat with SMOFlipid (40) or Soybean (40)	1 case of severe ROP ≥ stage in both groups; relative risk of 1.00 (0.06 to 15.44)	
Vlaardingerbroek *et al*., 2014[19]	RCT, I	96	Infants with BW <1500 were randomized to treat with SMOFlipid (48) or Soybean (48)	2 cases of severe ROP ≥ Stage 3 in control group and no occurrence in fish-oil group; relative risk of 0.20 (0.01 to 4.06)	
D'Ascenzo *et al*., 2014[11]	RCT, I	80	Infants with BW <1250 were randomized to treat with SMOFlipid (39) or Soybean (41)	No occurrence of severe ROP ≥ Stage 3 in both groups; Relative risk was not estimable	
Kapoor *et al*., 2015[12]	Meta-analysis, I	256	Three studies met the criteria for meta-analysis comparing all fish-containing lipid emulsions and control group but with low quality of evidence	The pooled relative risk of 0.43 (0.06 to 2.85) for severe ROP ≥ stage 3	
Vayalthrikkovil *et al*., 2017[18]	Meta-analysis, I	187 (RCTs) 192 (observational study)	Four RCTs and two observational studies met the criteria for meta-analysis	The pooled relative risk of 0.47 (95% CI: 0.24-0.90) for the need for ROP treatment and 0.40 (95% CI: 0.22-0.76) for severe ROP ≥ stage 3	+
Najm *et al*., 2017[13]	RCT, I	78	Infants with GA <28 were randomized to treat with SMOFlipid (41) or Clinoleic (37)	No difference between treatment groups in any ROP or severe ROP (≥3) development; *P* value 0.4 and 0.29, respectively	
Unal *et al*., 2018[17]	Prospective observational, II	205	Treated infants (SMOFlipid: 85, Clinoleic: 120) were evaluated for clinical outcomes such as ROP	No difference between treatment groups in any ROP or severe ROP (≥2) development; *P* value 0.63 and 0.60, respectively	

GA: Gestational age, BW: Birth weight, ROP: Retinopathy of prematurity, RCTs: Randomized clinical trials, CI: Confidence interval

It is established that in preterm infants who lack serum DHA as the main DHA lipid, storage time is between 26 and 40 weeks of GA, the time where they are not supplied by placental blood.[19,28] Considering neurodevelopment, including sensory, motor, and cognitive maturation[22] whether it has a protective effect on the prevention of ROP or not, supplying preterm infants (especially very low BW infants) with DHA-containing lipids would be appropriate. This study showed no reduction in the need for the treatment in ROP infants who received SMOFlipid compared to INTRAlipid infusion; however, fewer infants with severe ROP (Stage 3) were observed in the SMOFlipid-treated group.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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