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Research Article
Published: 08 Sep, 2016

The Role of Omega-3 Enriched Diet in the Development and Severity of Retinopathy of Prematurity (ROP)

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Abstract

To evaluate the impact of Omegaven on the development of ROP, we reviewed charts from 170 preterm infants who developed ROP from 01/2010 – 04/2014. All infants were started with standard parenteral lipid emulsion (Intralipid). Of these patients, 134 continued with Intralipid (group 1), 36 discontinued intralipid, and of these 36, 20 received Omegaven at ≤32 weeks PMA (Postmenstrual age) (group 2) and 16 received Omegaven at >32 weeks PMA (group 3). The association between Omegaven and ROP progression was analyzed with ANOVA and Pearson's Coefficient. The results showed that birth weights among all 3 groups were similar. The average PMA of ROP diagnosis in weeks was 33.1 ± 0.3 in group 1, 34.8 ± 2.6 in group 2, and 33.0 ± 0.6 in group 3 (p=0.002, groups 1, 2; p=0.8, groups 2, 3; p=0.15, groups 1, 3). Forty-four infants from group 1 (33%, 44/134) required laser photocoagulation treatment for ROP, while 10 infants (50%, 10/20) and 8 infants (50%, 8/16) in groups 2 and 3 respecfully, required ROP treatment. Average age of ROP treatment was 37.1 ± 3.6, 36.9 ± 3.6, and 36.9 ± 0.8 weeks respectively (p=0.5, groups 1, 2 and 1, 3). This study suggests that administration of an omega-3 enriched lipid emulsion postponed development of ROP but did not reduce the severity of ROP.

Keywords: Retinopathy of Prematurity; Omega-3-polyunsaturated Fatty Acids; Omegaven

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Received Date: *24 Jun 2016*
Accepted Date: *11 Jul 2016*
Published Date: *08 Sep 2016*

Citation:
Rahman EZ, Abrams SA, Hawthorne KM, Kong L. The Role of Omega-3 Enriched Diet in the Development and Severity of Retinopathy of Prematurity (ROP). Remed Open Access. 2016; 1: 1013.

Introduction

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness in the United States and worldwide [1], with an incidence rate of approximately 30% in preterm infants born at or earlier than 32 weeks gestation. Due to both the limited instances in which current therapy can treat ROP and the side effects involved with treatment, developing methods to prevent ROP are paramount [2]. The key to prevention lies in reducing the hyperoxic-hypoxic damage to immature retinal vessels.

Recently, omega-3-polyunsaturated fatty acids (PUFA) have been of interest due to their anti-inflammatory properties. A prior study by Connor et al. [3] demonstrated that increasing omega-3 PUFA levels by either dietary supplementation or genetic alteration stimulated vessel regrowth after injury and decreased the incidence of avascular regions within the retina. Arachidonic acid (ARA: C20: 4w-6) and docosahexenoic acid (DHA: c22: 6w-3) are derivatives of PUFAs and are necessary for proper retinal function. Uauy et al. [4] recently found that neonates are better at converting essential fatty acids into EPA, DHA and ARA than term infants are. However, these infants are still at an increased risk for DHA and ARA deficiencies due to their decreased stores and increased needs relative to term infants. Moreover, the process of maternal PUFA transfer begins during the third trimester, further adding to the omega-3 PUFA deficiencies in premature infants when compared to infants born at term [5].

Early studies utilizing oxygen-induced retinopathy in mouse models also demonstrated that a lower ratio of (omega−6)/(omega−3) PUFA supplementation decreased the hypoxic stimulus for neovascularization [6]. These preliminary results suggest that omega-3 PUFAs could be considered an adjuvant or preventive therapy for ROP.

Commonly used parental lipids such as Intralipid are rich in omega-6 PUFAs but essentially void of omega-3 PUFAs. We hypothesize that providing preterm infants with omega-3 enriched parenteral nutrition would prevent or delay ROP and consequently reduce the need for treatment. In this study, we retrospectively evaluated the effects of replacing Intralipid (Baxter Healthcare Corporation, Houston, TX) with Omegaven (Fresenius Kabi, Höhe, Germany) on the development

of ROP in gestation age (GA) and birth weight (BW) matched infants.

Methods

Study subjects

The study followed the tenets of the Declaration of Helsinki and was approved by the institutional review board (IRB) of Baylor College of Medicine. Due to the retrospective nature of the study, parental informed consent was waived. Total of 170 preterm infants who developed ROP from January 2010 to April 2014 were identified.

As described above, the following data were collected: GA, BW, ROP status, PMA at both time of diagnosis and treatment, start date of Intralipid or Omegaven, primary medical diagnoses, and presence or absence of complications including septicemia, intraventricular hemorrhage, bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC). In this study, all premature infants were screened for ROP followed ROP screening guidelines [7]. ROP was graded using the International Classification of ROP criteria [8]. The criteria for the treatment of severe ROP followed ET-ROP guidelines [9].

Statistics

Statistical analyses were performed using IBM SPSS software version 21 (IBM software, USA) and Graph Pad prism 5 (Graph Pad Software, USA). Generalized Estimating Equation (GEE) models were used to analyze the relationships among variables. One-way analysis of variance (ANOVA) with a post-hoc multi-comparison test was used to compare the three groups of data. Comparisons among variables were adjusted for GA and birth weight. Pearson correlation co-efficiency analysis was used to determine the correlation between PMA in which Omegaven was initiated and the PMA in which ROP was first diagnosed and treated. Fisher's exact test was used for proportions. Confidence interval level was 95%. A p-value less than 0.05 was considered statistically significant.

Results

Lipid emulsion distribution and patient clinical characteristics

This study included 170 infants who developed ROP of any stage. All infants were started with the standard parenteral lipid emulsion comprised of Intralipid, a soybean-derived, omega-6 predominant fatty acid at a rate of 10g/100mL. Of these infants, Intralipid was discontinued in 36 (21%) infants when the option of compassionate use of Omegaven was presented to parents of infants who developed cholestitis. The remaining 134 patients (79%) continued to receive standard Intralipid as seen in (Figure 1). The composition of both lipid emulsions is listed in (Table 1). Omegaven was delivered intravenously at 1g/kg/day and Intralipid was run at a standard weight-based regiment that varied per patient with an average goal of 3g/kg/day. The Omegaven provided 10 kcal/kg/day and Intralipid provided 10-30 kcal/kg/day.

Of the 36 patients who received Omegaven, 20 started Omegaven at ≤ 32 weeks (26.0 to 32.0) PMA (group 2) and 16 started Omegaven at >32 weeks (32.1 to 36.0) PMA (group 3). The mean GA and BW amongst these three groups were similar (Table 2).

ROP status

The average PMA of ROP diagnosis was significantly different between group 1 and group 2, with an average of 33.1 ± 0.3 weeks in group 1 and 34.8 ± 2.6 weeks in group 2 (p=0.002), as shown in (Table 2). However, there was no significant difference between group 1 and group 3 (p = 0.8) and between group 2 and group 3 (p=0.15). Forty-four infants from group 1 (33%, 44/134) required laser photocoagulation treatment for ROP, while 10 infants (50%, 10/20) and 8 infants (50%, 8/16) in groups 2 and 3 required ROP treatment. p value was 0.1 for group 1 and group 2, and 0.2 for group 1 and group 3.

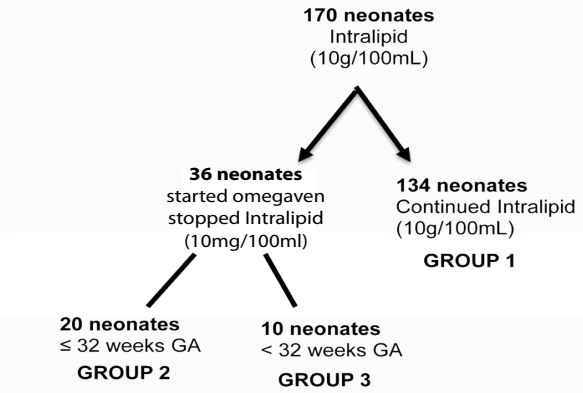

Figure 1: Distribution of Neonates to Omegaven and Intralipid Groups. One-hundred and seventy neonates were divided amongst 3 groups consisting of Intralipid (Group 1), 10% Omegaven ≤ 32 weeks PMA (Group 2) and 10% Omegaven >32 weeks PMA (Group 3).

The average age at which treatment was performed for severe ROP was similar amongst these three groups (Table 2) with a mean of 37.1 ± 3.6 weeks in group 1, 36.9 ± 3.6 weeks in group 2 (p=0.5) and 36.9 ± 0.8 weeks in group 3 (p=0.8). There was a positive correlation between Omegaven initiation at an earlier PMA and ROP diagnosis at a later PMA (r = 0.2, 95%; CI = -0.256 to 0.548).

Discussion

Our study suggests that administration of an intravenous omega-3 enriched lipid emulsion at less than 32 weeks PMA postponed ROP development for about 1.7 weeks, but did not reduce the severity of the disease nor the need for treatment. Interestingly, more infants in the Omegaven group required laser treatment. Omega-3 PUFAs help reduce the hyperoxic-hypoxic damage to the retina through the production of cytoprotective and anti-inflammatory mediators such as neuroprotectins and resolvins. These metabolites suppress TNF-

Table 1: Comparison of Intralipid and Omegaven Parenteral Fat Emulsion Components.

Product	Intralipid	Omegaven
Source	Soy	Fish Oil
Omega Fatty Acid	20% Omega-6	10% Omega-3
Oil source (grams)		
Soybean	10	0
Fish	0	10
Fat Composition (%)		
Linoleic	50	0.10 - 0.70
Alpha-Linoleic	9	<0.20
Eicosapentaenoic Acid	0	1.28 - 2.82
Docosahexenoic acid	0	1.44 - 3.09
Oleic	26	0.60 - 1.30
Palmitic	10	0.25 - 1.00
Stearic	3.50	0.05 - 0.20

Table 2: Comparison of Omegaven vs. Intralipid Lipid Emulsion Treatment Groups.

	Group 1 (134 pts)	Group 2 (20 pts)	Group 3 (16 pts)
Lipid Emulsion	Intralipid	Omegaven	Omegaven
Mean birth weight (g)	817 ± 294	811 ± 238	848 ± 317
[a]PMA of [b]ROP diagnosis (weeks)	33.1 ± 0.3*	34.8 ± 2.6*	33.0 ± 0.6
[c]Proportion of ROP treated %, (n/n)	33%, (44/134)	50%, (10/20)	50%, (8/16)
PMA of ROP treatment (weeks)	37.1 ± 3.6	36.9 ± 3.6	36.9 ± 0.8

Characteristics of each group: Group 1 = Intralipid standard lipid emulsion comprised of 20% omega-6 fatty acids; groups 2,3 = Omegaven alternative lipid emulsion comprised of 10% omega-3-polyunsaturated fatty acids. [a]PMA = postmenstrual age; [b]ROP = retinopathy of prematurity; [c]Number treated = number of infants treated with laser photocoagulation. *Denotes statistical significance (p≤ 0.05) compared to patients receiving Intralipid alone. Only PMA of ROP diagnoses between groups 1 and 2 was significant (p=0.002).

alpha and are increased in direct proportion to DHA [3]. In animal models of oxygen-induced retinopathy, it was found that Omega-3 PUFAs induced protection against retinopathy due to its effects in reducing vascularized within the retina. It did not prevent the vaso-obliteration induced by the hyperoxic damage nor did it suppress the expression of VEGF, which is the major growth factor for ROP [3]. This explains the postponed development of ROP found in our study; however, it did not reduce the severity of ROP.

In an observational study by Pawlik et al. [10], 40 preterm infants received Omegaven at doses of 0.15 – 0.35 g/kg/day, up to 1.0–1.2 g/kg/day starting on the first day of life. Forty four control infants received a lipid emulsion consisting of 20% soybean and 20% olive oil. They found that the occurrence rate of ROP between the two groups were similar 13 (32.5%) in the experimental group *vs*. 16 (36.5%) in the control group. This study also reported spontaneous ROP regression in 10/13 (77%) patients in the experimental group and a lower indication for laser therapy in these patients. Due to the retrospective nature of our study, none of our subjects in this study received Omegaven from the first day of life. However, infants who received Omegaven before 32 weeks PMA developed a delayed onset of ROP by 1.7 weeks. This delay provides valuable time for neuronal retinal development.

In addition to DHA, EPA another component of Omegaven, may also reduce inflammatory signals. This same study demonstrated that EPA diminishes the rate of VEGF tyrosine kinase receptor activation. With decreased VEGF, mediators that encourage vascular instability, such as COX-2, nitric oxide, thrombin and intracellular adhesion molecules are down-regulated [11]. The Omegaven used in this study was designed to treat short bowel syndrome and associated cholestatic complications. Because Omegaven having been optimized for these particular medial problems, NHO of DHA to EPA ratio may not be ideal for the prevention of ROP.

One limitation of our study includes the retrospective nature of our review resulting in a disproportionate, non-randomized allocation of infants to either the Omegaven or Intralipid groups. A properly designed randomized clinical trial is necessary to study the roles of Omegaven in the development of ROP. Future studies regarding intravenous omega-3 PUFAs in preterm infants should focus on regulating proportions amongst individual omega-3 components, such as the proportion of DHA to EPA in order to identify an ideal balance to reduce the severity of ROP. In addition to the composition, identifying the ideal time for initiation of treatment is necessary as well.

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