Effects of Adjuvant Administration of Macromolecules and Total Calories through Aggressive Parenteral Nutrition in Improvement of Neovascularisation of Infants with Retinopathy of Prematurity: A Literature Review

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ABSTRACT

Introduction: Retinopathy of Prematurity (ROP) is almost exclusively in premature infants. With advanced care and technology, the prevalence of retinopathy of prematurity in babies is increasing, which means the incidence of preventable blindness in ROP is increasing. Objectives: To evaluate the effects of protein, glucose, lipids, and total calories from Aggressive Parenteral Nutrition (APN) in improving neovascularisation of ROP in premature infants. Methods: We searched PubMed, Ophthalmology Advance, Scientific Reports, and Science Direct using the terms "Retinopathy of Prematurity", "Aggressive Parenteral Nutrition", "Prevalence of Retinopathy of Prematurity in Indonesia", "Protein", "Lipid", "Carbohydrate", "Glucose", "Total Calories", "Neovascularization", and "Prematurity" in various combinations. Results: We found three pieces of literature stating a positive association between APN and improvement of ROP, while one literature states that there is no significant change of prevalence of ROP by administering APN.

Keywords: Aggressive Parenteral Nutrition, glucose, lipid, protein, Retinopathy of Prematurity

INTRODUCTION

Retinopathy of prematurity is a vasoproliferative retinal disorder unique to premature infants in which there is an abnormal growth of retinal blood vessels due to a complex interaction between vascular endothelial growth factor and insulin-like growth factor 1.[1] Retinal
vascular development begins during the 16th week of development and its distribution reaches nasal ora serrata by 36 weeks' gestation where its development is interrupted by preterm birth and may develop retinopathy of prematurity (ROP) as its consequence.[1,2]

The incidence and severity increase with decreasing gestational age and birth weight.[3–7] Next to cortical blindness, retinopathy of prematurity is the most common cause of childhood blindness worldwide.[8,9] The incidence of retinopathy of prematurity is increasing due to the increased survival rate of premature neonates due to better care and advancement in technology.[10,11] The incidence rate of retinopathy in prematurity in Rumah Sakit Umum Pendidikan Cipto Mangunkusumo in 2007 is 20.22% out of 71% premature babies.[9] Ocular outcome is typically poor in infants with severe untreated ROP, with all infants with a poor structural outcome and nearly all poor visual acuity outcome having a history of severe ROP.[9]

Some recent evidence demonstrated that inadequate nutrition in premature infants in the first week results in growth retardation and may lead to permanent detrimental effects such as blindness due to retinopathy of prematurity.[13,14] Insufficient nutrition during the first four postnatal weeks results in low serum levels of IGF-1, which is essential for correct retinal vessels formation, ensuring the survival of the newly formed endothelial cells. Keeping the newborns in a positive energetic balance by providing enough nutrients and energy has a beneficial impact on their growth, neurodevelopment, and decreasing incidence of ROP. The best way to achieve this is early parenteral nutrition with the high content of nutrients combined with early enteral feeding by one's mother's breast milk.[2,15]

This study aims to evaluate the effects of each protein, glucose, lipid as macromolecules, and total calories in improving the vascularisation of premature infants with retinopathy of prematurity while analysing whether they are clinically significant.

**METHOD**

We searched PubMed, Ophthalmology Advance, Scientific Reports, and Science Direct using the terms "Retinopathy of Prematurity", "Aggressive Parenteral Nutrition", "Prevalence of Retinopathy of Prematurity in Indonesia", "Protein", "Lipid", "Carbohydrate", "Glucose", "Total Calories", "Neovascularization", and "Prematurity" in various combinations. The search was conducted on the 20th of December 2019. We included ten years old literature from all levels of evidence, had full paper access, and only included human studies. Exclusion criteria are animal studies and infants with hydrocephalus or major congenital anomalies included in the studies and infants under 22 weeks of age. We found 12 studies with four studies from PubMed, 2 with Scientific Reports, 2 with Ophthalmology Advance and 4 with Science Direct. One was excluded as it was published in 2006, 1 did not specify the total carbohydrate parenterally, one studied only about lipid, one studied only about vitamins and breast milk, one studied only about amino acids, one studied only about amino acid and lipid together, and two studies only provided discussion without data. In the end, we selected four pieces of literature as our discussion materials.

**DISCUSSION**

After assessing the inclusion and exclusion criteria mentioned above, we analysed four literature enrolling 1781 infants. Three studies were done with prospective cohort study, whereas 1 study was done in a randomised clinical trial. From 4 studies, 3 found a significant relationship between the administration of...
aggressive parenteral nutrition with ROP incidence. Aggressive parenteral nutrition was given in the form of protein, lipid, and glucose, with a bigger amount given earlier when compared with the conventional parenteral nutrition group. The characteristics of each study are shown in Table 1, while the characteristics of calories, glucose, lipid, and protein used by each study are shown in Table 2, 3, 4 and 5.

Liu et al. (2015) explained no correlation between the administration of aggressive parenteral nutrition and retinopathy of prematurity. In this prospective cohort research, 13 infants were given aggressive parenteral nutrition, and 15 were given conventional parenteral nutrition. One patient from the aggressive parenteral nutrition group developed ROP, while one patient from the conventional parenteral nutrition group also developed ROP. Therefore, the study found no association between the two variables. It should be noted that this study has a minimum amount of sample for a prospective cohort study that may explain the lack of connection between the two variables. In addition, the researcher defined aggressive parenteral nutrition quite differently from other studies. Aggressive parenteral nutrition in this regard was defined as giving the same amount of protein, lipid, and glucose as the conventional group. However, it was given earlier, that is, on the first day of life, while the conventional group was given during the third day of life.

Nevertheless, this study amplifies the need for addition in the amount of nutrition given, rather than only giving it earlier, to prevent the incidence of retinopathy of prematurity. The mechanism of how the amount of nutrition given could affect the incidence of ROP will be discussed later. On the other hand, three other studies, which comprise of 1 randomised clinical trial and two prospective cohort studies, state that there is a positive correlation between aggressive parenteral nutrition and ROP.

Aggressive parenteral nutrition in premature neonates is one of the most important treatment regimes in early life. Parenteral nutrition (PN) could be the best option for premature infants because of prematurity-associated morbidities such as respiratory distress syndrome, hypotension, temperature instability, gut immaturity, and surgical lesions that preclude enteral nutrition, are usually not feasible to initiate enteral feeds immediately after birth. Therefore, PN should be initiated as soon as possible after birth, either through the umbilical or peripheral venous line. In the past 20 years, the practice of PN has been to increase the amount of amino acids intake gradually and shorten the time after birth to start parenteral alimentation. The administration of amino acids during the first hours of life aims to reach fetal nutrient delivery rates and is the key to avoiding early neonatal malnutrition. Amino acids are important in synthesising insulin, insulin-like factors, and other growth-related hormones. Dosage may be increased from 0 g/kg/d to 4 g/kg/d, where earlier and higher IV amino acid administration rates need to be given immediately after birth for preterm infants. Several controlled studies have shown the efficacy and safety of amino acids when given in the first 24 hours of life.

Early administration of lipids is important to meet essential fatty acid (EFA) requirements and high energy in preterm infants due to limited endogenous lipid stores. Lipids are suitable for administration through a peripheral vein since there is no significant increase in fluid load. During the third trimester, a massive transfer of long-chain polyunsaturated fatty acids (LCPUFAs) occurs from the mother to the fetus. Docosahexaenoic acid (DHA) and omega 3- LCPUFA, derived from cold water algae and oily fish, are the predominant fatty acid of membrane phospholipids in...
the brain grey matter and the retina, and
the only omega-3-LCP UF present in
significant amounts in the brain.\textsuperscript{[22]} The
American Academy of Pediatrics
recommended early initiation of lipids on
the first or second day of life at a low dose
0.5-1 g/kg/d, gradually increasing to 3-3.5
g/kg/d, and with slow infusion over 20-24
hours period. However, there should be
caution in administering lipid because
EFA clearance in preterm infants is slower
than in term infants. Elevated EFA
concentration may displace bilirubin from
albumin binding sites and increase free or
unbound bilirubin concentration. This
unbound bilirubin can cross the blood-
brain barrier and cause brain injury and
neurotoxicity. Infants with bilirubin of 8-
10 mg/dL and albumin of 2.5-3 g/dL can
safely receive IV lipid emulsion of 0.5-1
g/kg/d.\textsuperscript{[21]}

Glucose is a major energy source for
the immature brain. It also serves as a
substrate for synthesising fatty acids and
nonessential amino acids, where the
energy released by 1 gram is 4 kcal.
Preterm infants have higher endogenous
glucose production than healthy term
infants. It may reach up to 8.3 mg/kg/min,
and to match this increased endogenous
production, an adequate intake of
intravenous glucose is 6-8 mg/kg/min
started shortly after birth. However,
careful monitoring of glycemic status is
essential since it might cause
hyperglycemia. Higher serum glucose
concentration may increase serum
osmolarity osmotic diuresis and increase
fat deposition resulting in liver steatosis
since the excess of glucose is stored as
fat.\textsuperscript{[21]}

Some recent evidence has shown that
preterm infants’ inadequate nutrition in
the first week results in growth retardation
and may lead to permanent detrimental
effects. Therefore, parenteral nutrition
is required until full enteral nutrition can be
established. Balanced parenteral nutrition
with an early and “aggressive” approach is
important for preterm infants to minimise
postnatal weight loss, promote an earlier
return to birth weight, and lessen
erutine growth restriction.\textsuperscript{[20]}
Extrauterine growth retardation is
associated with adverse outcomes,
including chronic lung disease, increased
risk of infection, severe retinopathy, and
abnormal neurodevelopmental outcome.
To achieve a weight gain of preterm
infants appropriate for gestational age
without any adverse effects, there should
be no interruption in the delivery of
nutrients from birth and adequate PN to
minimise weight loss and improve growth.
The European Society of Pediatric
Gastroenterology, Hepatology and
Nutrition (ESPGHAN) has recommended
caloric intake of 110 to 120 kcal/kg/day
for infants who are parenterally fed.
However, it is difficult to achieve this
standard caloric intake because of fluid
restriction, intolerance to the suggested
glucose infusion rate, delay in initiation of
parenteral amino acid solutions,
immaturity of intestinal functions, and
slow progression of enteral feeding.\textsuperscript{[21]}
Man Yau Ho (2016) stated that the
principles of nutritional practice should
include early initiation of enteral feeding
with breast milk 0.5-1 mL/h and gradual
advance as tolerated, early aggressive PN
as soon as possible, and early introduction
of IV lipid emulsion 0.5-1 g/kg/d,
gradually increasing to 2-3 g/kg/d.\textsuperscript{[21]}

Retinopathy of prematurity mostly
developed in premature infants below
1500 grams and 32 weeks gestational
age.\textsuperscript{[12]} ROP develops in two phases. The
first phase is vasoobliterative, caused by
interrupted and delayed angiogenesis. The
levels of hypoxia-inducible factors (HIF),
vascular endothelial growth factor (VEGF),
insulin-like growth factor (IGF-1), and
eythropoietin (EPO) are all
decrease during this phase.\textsuperscript{[22]} This phase
begins after preterm birth and involves
growth cessation of the retina vasculature.
As the newborn grows, there is a
significant increase in metabolic demands,
and lately, the retina starts to become hypoxia, which upregulates the synthesis of VEGF with its subsequent accumulation in the retina and the vitreous body. Suppose the nutrition is insufficient in this stage. In that case, serum levels of IGF-1 are low, and angiogenesis does not occur effectively even if VEGF is present, since, without IGF-1, the endothelial cells undergo excessive apoptosis. The second phase includes vasoproliferative phase of ROP at around 32-34 weeks of postconceptional age. These two phases are further described in Figure 1. A sufficient caloric intake and adequate nutrients can prevent the postnatal gap in weight gain and IGF-1 levels and thus promote catch-up growth and development in preterm infants.[22]

**Figure 1. Major Pathway in ROP**

In preterm infants, endothelial cells that play a key role in vasculogenesis and angiogenesis produce IGF-1. Hypoxia is a major angiogenic stimulus that increases vascular endothelial growth factor (VEGF) mRNA transcription.[23] IGF-1 may also increase VEGF-1 synthesis. Minimal levels of IGF-1 are required for VEGF activation of pathways promoting retinal vascular endothelial cell proliferation and survival.[24] Impaired normal neonatal angiogenesis after preterm birth followed by tissue hypoxia and nutrient insufficiency driving proliferative angiogenesis is a hallmark of ROP.[25] A strong correlation was found between serum IGF-1 levels during the first week of life and later ROP development.[26] Serum IGF-1 could be used to predict the risk of infants developing severe ROP. ROP screening programs generally include infants based on gestational age (GA) at birth and/ or birth weight (BW). Based on longitudinal weight and IGF-1 development after birth, the algorithm Weight IGF-1 Neonatal ROP (WINROP) was developed.[27]

IGF-1 level is a nutrition dependent parameter. The bioavailability of IGF-1 is regulated by insulin growth factor binding protein (IGFBP).[17] Based on previously published studies, low energy intake during the first four weeks of life can lead to arrested vascularisation either through a decrease in IGF-1 alone or combination with a decrease in other angiogenic promoting factors or poor nutrient supply to the growing vessels.[27] Undernutrition concerning energy and/or protein is known to reduce plasma levels of IGF-1, but there should be a threshold energy requirement under which the protein intake does not increase IGF-1, as shown in Figure 2.[28]

First, IGF-1 is required for VEGF activation, thus resulting in the proliferation of vascular endothelial cells. IGF-1 is transferred to the infant during pregnancy, and with preterm birth, the infant will suddenly face a rapid fall of serum IGF-1 due to the loss of connection to maternal sources.[17] This phenomenon results in the impairment of retinal neovascularisation and disrupts normal angiogenesis, leaving it avascular and
prompting ROP onset. Can et al. (2012) conclude that the lack of IGF-1 in the early weeks of life, followed by a slow increase, suggest a larger risk of developing ROP. Next, infants with lower IGF-1 levels are more likely to develop ROP, thus heightening the urgency for restoration of IGF-1 level to prevent ROP. A study conducted by Can et al. (2013) found that while giving conventional and aggressive parenteral nutrition resulted in no difference for mean weight gain, the levels of IGF-1 and IGFBP3 on the two groups were distinct, with higher results found in those given aggressive parenteral nutrition than in conventional parenteral nutrition proven by a significant p-value. It was also found that IGF-1 levels should reach above certain cutoff value in order to prevent ROP. A study by Hellstrom et al. (2009) found that preterm infants between 30-35 weeks of gestation have a risk of developing ROP stage 2-5 when IGF-1 levels were lower than 30 ng/ml. On the other hand, at postnatal 4-6 weeks, IGF-1 levels lower than 24 ng/ml were related to ROP. Therefore, it is apparent that IGF-1 is lower without any proper feeding practices. When early nutrition is given, the IGF-1 level rises.

The added amount of nutrition provides more substrates for the synthesis of proteins, including proteins that take a great role in ROP, IGF-1. First, lipid provides high energy levels, enabling the body to use it as a sufficient energy source for protein synthesis without further oxidising amino acids. Second, several studies show that amino acid administration may transform negative nitrogen balance to positive balance, thus promoting anabolism. Vlaardingerbroek et al. conclude that at least one half of the extra administered amino acid was used for anabolism. However, amino acid and lipid are given in high amounts simultaneously, amino acid oxidation increases. It was found that the urea production rate was significantly higher in this group, which suggest the oxidation of excess amino acid that was not used for protein synthesis as the body's mechanism to prevent hyperaminoacidemia. An increase in protein synthesis will increase the production of hyperaminoacidemia. Therefore, it is hypothesised that through this mechanism, the administration of aggressive parenteral nutrition will eventually help prevent ROP development. Nevertheless, early lipid initiation and high-dose amino acids were well tolerated, with no increased incidence of adverse events, proven with normal haematology, biochemistry, and plasma amino acid concentrations compared to healthy term breastfed infants.

**RECOMMENDATIONS**

In conclusion, keeping the newborns in a positive, energetic balance by providing enough nutrients and energy has a beneficial impact in decreasing ROP incidence through improving neovascularisation of ROP. Aggressive parenteral nutrition provided a decreased loss of amino acids in premature infants on the first day of life. With higher levels of protein synthesis, IGF-1 level will rise as well, therefore enabling the development of neovascularisation that is important in the development of the retina in the early days of life. However, the authors suggest that in the future, literature will reach an agreement on the definition of “aggressive parenteral nutrition” such that it will be useful clinically. We want to acknowledge dr. Werlinson Tobing, SpM and dr. Andry Juliansen, SpA for their immense contributions.

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Effects of Adjuvant Administration of Macromolecules and Total Calories through Aggressive Parenteral Nutrition in Improvement of Neovascularisation of Infants with Retinopathy of Prematurity: A Literature Review

Table 1. Characteristics of Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Types of Studies</th>
<th>Outcome</th>
<th>P value of ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ming-Yi Liu et al (2015)</td>
<td>28 infants, 15 in conventional support group (CVS), 13 in aggressive support group (AGS) with a birth weight of &lt;1500 g and more than 750 g were eligible for the study</td>
<td>Prospective Cohort Study</td>
<td>No difference in prevalence of ROP in groups receiving CVS and AGS</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Emrah can, et al 2013</td>
<td>Preterm infants &lt;32 weeks, NGA 1:1 for conventional parenteral nutrition and aggressive parenteral nutrition 75 preterm infants</td>
<td>Prospective, randomized, double blind, clinical trial</td>
<td>ROP : 5% in APN group, 31.4% in CPN (5 with ROP stage 1), 6 in ROP stage 2 (p: 0.0004)</td>
<td>ROP incidence p value 0.004</td>
</tr>
<tr>
<td>Vanderveen et al (2013)</td>
<td>1180 infants, &lt;28 weeks GA birth with ROP examination. Measured on postnatal days 3, 7, 14, and 21.</td>
<td>Prospective cohort study.</td>
<td></td>
<td>P value significant for infants whose recept of the fat, calories at p value= 0.05</td>
</tr>
<tr>
<td>Elisabeth Stoltz Sjöström et al (2015)</td>
<td>All infants with a gestational age at birth of 22 weeks + 0 days to 26 weeks + 6 days born between 1 April 2004 and 31 March 2007 with ROP data were collected prospectively for all infants in the Extremely Preterm Infants in Sweden Study (EXPRESS) cohort as described previously. The final study cohort consisted of 498 infants.</td>
<td>A population-based cohort study</td>
<td>Lower fat and carbohydrate intake was associated with increased risk of developing severe ROP while protein intakes were only significantly associated with severe ROP during the fourth week</td>
<td>p value for fat is &lt;0.001, p value for carbohydrate is &lt; 0.01, p value for calories is &lt; 0.001 while p value for protein is &lt; 0.05</td>
</tr>
</tbody>
</table>
Effects of Adjuvant Administration of Macromolecules and Total Calories through Aggressive Parenteral Nutrition in Improvement of Neovascularisation of Infants with Retinopathy of Prematurity: A Literature Review

Table 2. Characteristics of Calories Used by Each Study

<table>
<thead>
<tr>
<th>Author</th>
<th>Parameter Used</th>
<th>Conventional Parenteral Nutrition (CPN)</th>
<th>Aggressive Parenteral Nutrition (APN)</th>
<th>P Value of ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ming-Yi Liu et al (2015)</td>
<td>kcal/kg/day</td>
<td>Week 1: 75.5 ± 11.2</td>
<td>Week 1: 85.5 ± 8.4</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 2: 81.6 ± 1.8</td>
<td>Week 2: 108.6 ± 13.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 3: 84.8 ± 11.0</td>
<td>Week 3: 108.6 ± 14.4</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 4: 90.8 ± 13.3</td>
<td>Week 4: 116.2 ± 14.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Emrah Can et al (2013)</td>
<td>Kcal/kg/day</td>
<td>115.5(28.5)</td>
<td>121.5 (35.5)</td>
<td>0.4</td>
</tr>
<tr>
<td>Emrah Can et al (2013)</td>
<td>kcal/kg/day</td>
<td>-</td>
<td>No ROP: 86 ROP: 78.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Elisabeth Stoltz Sjöström et al (2015)</td>
<td>Kcal/kg/day (10 kcal/kg/day increment)</td>
<td>Week 1-4: 102 (14)</td>
<td>Week 1: 66 (10)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Week 2: 102 (17)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Week 3: 116 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Week 4: 124 (21)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
### Table 3. Characteristics of Glucose Used by Each Study

<table>
<thead>
<tr>
<th>Author</th>
<th>Glucose Used</th>
<th>Parameter Used</th>
<th>Conventional Parenteral Nutrition (CPN)</th>
<th>Aggressive Parenteral Nutrition (APN)</th>
<th>P Value of ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ming-Yi Liu et al (2015)</td>
<td>Not Specified</td>
<td>g/kg/day</td>
<td>4 mg/kg/min of glucose, during the first 24 hours of life. The glucose infusion was increased progressively to a maximum of 6 mg/kg/min to maintain blood glucose levels less than 120 mg/dL starting from day 3</td>
<td>4 mg/kg/min of glucose, during the first 24 hours of life. The glucose infusion was increased progressively to a maximum of 6 mg/kg/min to maintain blood glucose levels less than 120 mg/dL starting from day 1</td>
<td>-</td>
</tr>
<tr>
<td>Emrah Can et al (2013)</td>
<td>Dextrose 2-%, 10% 5%, baxter/clinte c, maurepance, france®</td>
<td>g/kg</td>
<td>-</td>
<td>Started at 6-8 mg/kg/min during the first day of life and increased gradually to 12 mg/kg/min in order to maintain blood glucose concentration between 80-100 mg/dl while avoiding any hyperglycemia</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Vanderveen et al (2013)</td>
<td>Not Specified</td>
<td>g/kg/day</td>
<td>-</td>
<td>No ROP: 10 ROP: 7.53</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Elisabeth Stoltz Sjöström et al (2015)</td>
<td>Not Specified</td>
<td>g/kg/day (1 g/kg/day increment)</td>
<td>-</td>
<td>Week 1: 9.1 (1.3) Week 2: 11.3 (1.4) Week 3: 12.0 (1.6) Week 4: 12.4 (1.7)</td>
<td>&gt;0.05 &lt;0.05 &gt;0.05 &lt;0.05</td>
</tr>
</tbody>
</table>
Table 4. Characteristics of Lipid Used by Each Study

<table>
<thead>
<tr>
<th>Author</th>
<th>Lipid Used</th>
<th>Parameter Used</th>
<th>Conventional Parenteral Nutrition (CPN)</th>
<th>Aggressive Parenteral Nutrition (APN)</th>
<th>P Value of ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ming-Yi Liu et al (2015)</td>
<td>A 20% lipid solution, which is an equal mixture of medium-chain triglycerides and long-chain triglycerides (Lipofundin, B Braun Ltd®)</td>
<td>g/kg/day (0.5 g/kg/day increment)</td>
<td>Week 1: 3.75 ± 0.53</td>
<td>Week 1 : 4.03 ± 0.44</td>
<td>0.282</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Week 2: 3.88 ± 0.09</td>
<td>Week 2 : 5.2 ± 0.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Week 3: 3.87 ± 0.34</td>
<td>Week 3 : 5.33 ± 0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Week 4 : 4.23 ± 0.57</td>
<td>Week 4 : 5.74 ± 0.87</td>
<td>0.001</td>
</tr>
<tr>
<td>Emrah Can et al (2013)</td>
<td>Intralipid 20%, fresenius KABI, Uppsala, Sweden®</td>
<td>g/kg</td>
<td>6.1 (0.6)</td>
<td>6.6 (1.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Vanderveen et al (2013)</td>
<td>Intravenous fat emulsion (Intralipid®)</td>
<td>g/kg/day</td>
<td>-</td>
<td>No ROP: 1.6 ROP: 0.93</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Week 1: 2.2 (0.8)</td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Elisabeth Stoltz Sjöström et al (2015)</td>
<td>Purely soy-based lipid emulsion (Intralipid, Fresenius Kabi AB, Uppsala, Sweden®)</td>
<td>g/kg/day (1 g/kg/day increment)</td>
<td>Week 1-4: 4.8 (1.2)</td>
<td>Week 2: 4.7 (1.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Week 3: 5.8 (1.8)</td>
<td>&lt;0.01</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Week 4: 6.4 (1.9)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
### Table 5. Characteristics of Protein Used by Each Study

<table>
<thead>
<tr>
<th>Author</th>
<th>Protein Used</th>
<th>Parameter Used</th>
<th>Conventional Parenteral Nutrition (CPN)</th>
<th>Aggressive Parenteral Nutrition (APN)</th>
<th>P Value of ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ming-Yi Liu et al (2015)</td>
<td>10% amino acid solution (Aminosteril Infant Fresenius Kabi, Germany®)</td>
<td>g/kg/day (0.5 g/kg/day increment)</td>
<td>Week 1: 2.5 ± 0.6</td>
<td>Week 1: 3.1 ± 0.4</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Week 2: 3.0 ± 0.3</td>
<td>Week 2: 3.5 ± 0.4</td>
<td>0.047</td>
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<td>Week 3: 3.0 ± 0.3</td>
<td>Week 3: 3.3 ± 0.2</td>
<td>0.043</td>
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<td>Week 4: 3.0 ± 0.5</td>
<td>Week 4: 3.3 ± 0.2</td>
<td>0.157</td>
</tr>
<tr>
<td>Emrah Can et al (2013)</td>
<td>Primene 10%, baxter/clintec, Maureoance, France®</td>
<td>g/kg</td>
<td>3.2 (0.5)</td>
<td>3.52 (0.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Vanderveen et al (2013)</td>
<td>Not Specified</td>
<td>g/kg/day</td>
<td>No ROP: 3.52</td>
<td>ROP: 3.36</td>
<td>&gt;0.05</td>
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<td>Week 1: 2.2 (0.6)</td>
<td></td>
<td>&gt;0.05</td>
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<td>Week 2: 3.0 (0.5)</td>
<td></td>
<td>&gt;0.05</td>
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<td></td>
<td>Week 3: 3.3 (0.6)</td>
<td></td>
<td>&gt;0.05</td>
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<td>Week 4: 3.4 (0.7)</td>
<td></td>
<td>&lt;0.05</td>
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<tr>
<td>Elisabeth Stoltz Sjöström et al (2015)</td>
<td>Not Specified</td>
<td>g/kg/day (1 g/kg/day increment)</td>
<td>Week 1-4: 3.0 (0.4)</td>
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<td>Week 2: 3.0 (0.5)</td>
<td></td>
<td>&gt;0.05</td>
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<td></td>
<td>Week 3: 3.3 (0.6)</td>
<td></td>
<td>&gt;0.05</td>
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<td>Week 4: 3.4 (0.7)</td>
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<td>&lt;0.05</td>
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