SCRIPTA SCORE
Scientific Medical Journal

Literature Review

scripta

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

Stefany Tanto, Gilbert Sterling Octavius, Alvita Suci Edgina

¹Faculty of Medicine, University of Pelita Harapan, Karawaci, Tangerang, Banten, Indonesia

*Correspondence: stefany.tanto@yahoo.com

ABSTRAK

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

ABSTRACT

Pendahuluan: *Retinopathy of Prematurity (ROP) adalah penyakit yang hampir secara eksklusif terjadi pada bayi prematur. Dengan perawatan dan teknologi yang canggih, prevalensi retinopati pada bayi prematur meningkat dan ini berarti kejadian kebutaan yang dapat dicegah pada ROP meningkat.* ***Tujuan:*** *Untuk mengevaluasi efek protein, glukosa, lipid, dan kalori total dari Nutrisi Parenteral Agresif (APN) dalam meningkatkan neovaskularisasi ROP pada bayi prematur.* ***Metode:*** *Kami mencari PubMed, Ophthalmology Advance, Scientific Reports dan Science Direct menggunakan istilah "Retinopathy of Prematurity", "Aggressive Parenteral Nutrition", "Prevalence of Retinopathy of Prematurity in Indonesia", "Protein", "Lipid", "Carbohydrate" , "Glukosa", "Kalori Total", "Neovaskularisasi", dan "Prematuritas" dalam berbagai kombinasi.* ***Hasil:*** *Ditemukan tiga literatur yang menyatakan terdapat hubungan positif antara APN dengan peningkatan ROP sedangkan satu literatur menyatakan tidak ada perubahan signifikan prevalensi ROP dengan pemberian APN.*

Kata Kunci: Nutrisi Parenteral Agresif, glukosa, lipid, protein, Retinopati Prematuritas

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.[16] 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.[17-19]

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.[20] 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.[21]

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-LCPUFA present in significant amounts in the brain.[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.[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.[21]

Some recent evidence has shown that premature 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 extrauterine growth restriction.[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 a 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.[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.[21]

Retinopathy of prematurity mostly developed in premature infants below 1500 grams and 32 weeks gestational age.[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 erythropoietin (EPO) are all decrease during this phase.[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]
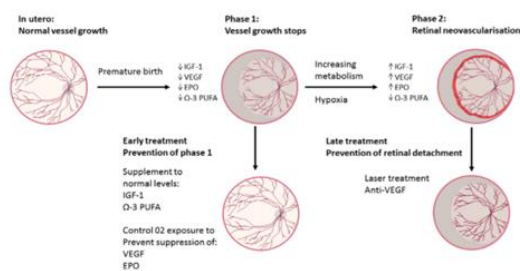

Figure 1. Major Pathway in ROP22

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]
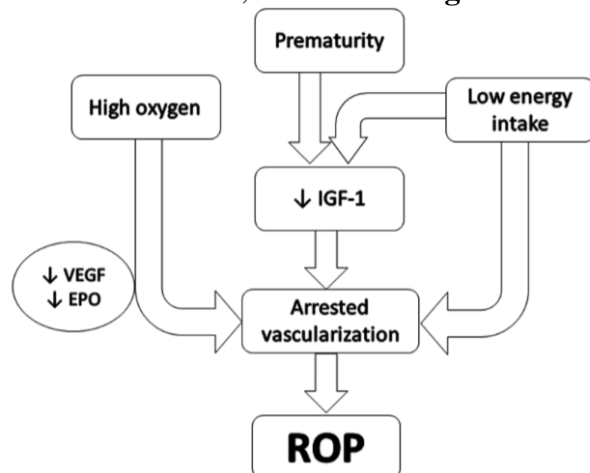

Figure 2. Proposed mechanism of the first phase of retinopathy of prematurity pathogenesis during the first four postnatal weeks.[28]

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.[29] 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.[17] 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.[30]

The added amount of nutrition provides more substances 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.[31] Vlaardingerbroek et al. conclude that at least one half of the extra administered amino acid was used for anabolism.[32] 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 IGF-1 as well. 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.[32]

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.[24] 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.

REFERENCES

[1] American Academy of Ophthalmology. Pediatric Ophthalmology and Strabismus. Section 6. 2014-2015.
[2] Lenhartova N. Matasova K. Lasabova Z. Javorka K. Calkovska A. Impact of Early Aggressive Nutrition on Retinal

Development in Premature Infants. Institute of Physiology of the Czech Academy of Sciences, Prague, Czech Republic. April 30, 2017.

[3] Hussain N, Clive J, Bhandari V. Current incidence of retinopathy of prematurity, 1989-1997. Pediatrics 1999; 104:e26. 23.

[4] Palmer EA, Flynn JT, Hardy RJ, et al. Incidence and early course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Ophthalmology 1991; 98:1628.24.

[5] Darlow BA, Hutchinson JL, Henderson-Smart DJ, et al. Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. Pediatrics 2005; 115:990.

[6] Haines L, Fielder AR, Baker H, Wilkinson AR. UK population based study of severe retinopathy of prematurity: screening, treatment, and outcome. Arch Dis Child Fetal Neonatal Ed 2005; 90:F240.

[7] Todd DA, Wright A, Smith J, NICUS Group. Severe retinopathy of prematurity in infants <30 weeks' gestation in New South Wales and the Australian Capital Territory from 1992 to 2002. Arch Dis Child Fetal Neonatal Ed 2007; 92:F251.

[8] World Health Organization. WHO media centre: Visual impairment and blindness. 2014 Agu [cited 2018 Jan 2]. Available from: http://www.who.int/mediacentre/factsheets/fs282/en

[9] David KC. Retinopathy of prematurity: Pathogenesis, epidemiology, classification, and screening. UptoDate. Last Updated: June 01, 2017.

[10] Gilbert C, Muhit M. Twenty years of childhood blindness: What have we learnt?. J Comm Eye Health 2008;21:46-7.

[11] Wheatley C, Dickinson J, Mackey D, Craig J, Sale M. Retinopathy of prematurity of prematurity: Recent advances in our understandings. Arch Dis Child Fetal Neonatal 2002;87:F78-F82.

[12] Lukitasari A. Retinopati pada prematuritas. Jurnal Kedokteran Syiah Kuala 2012;12:118-21.

[13] Ehrenkranz RA. Early, aggressive nutritional management for very low birth weight infants: what is the evidence? Semin Perinatol. 2007;31(2):48-55. 3.

[14] Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics. 2001;107:270-273.

[15] Fang JL, Sorita A, Carey WA, et al. Interventions To Prevent Retinopathy of Prematurity: A Meta-analysis. Pediatrics. 2016;137(4):e20153387

[16] Liu M, Chen Y, Hu S, Chen Y, Chang S. The Influence of Aggressive Parenteral Nutrition to Preterm and Very Low Birth Weight Infants. Global Pediatric Health. 2015;2:2333794X1456719.

[17] Can E, Bülbül A, Uslu S, Bolat F, C.mert S, Nuhoğlu A. Early aggressive parenteral nutrition induced high insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP3) levels can prevent risk of retinopathy of prematurity. Iran J Pediatr. 2013;23(4):403–410.

[18] VanderVeen D, Martin C, Mehendale R, Allred E, Dammann O, Leviton A. Early Nutrition and Weight Gain in Preterm Newborns and the Risk of Retinopathy of Prematurity. PLoS ONE. 2013;8(5):e64325.

[19] Stoltz Sjöström E, Lundgren P, Öhlund I, Holmström G, Hellström A, Domellöf M. Low energy intake during the first 4 weeks of life increases the risk for severe retinopathy of prematurity in extremely preterm infants. Archives of

Disease in Childhood - Fetal and Neonatal Edition. 2015;101(2):F108-F113.

[20] Patel P, Bhatia J. Total parenteral nutrition for the very low birth weight infant. Seminars in Fetal and Neonatal Medicine. 2017;22(1):2-7.

[21] Ho M, Yen Y. Trend of Nutritional Support in Preterm Infants. Pediatrics & Neonatology. 2016;57(5):365-370.

[22] Hård AL, Smith LE, Hellström A: Nutrition, insulin-like growth factor-1 and retinopathy of prematurity. Sem Fetal Neonatal Med 18: 136-142, 2013.

[23] N. Eter, M. Sahm, D. Kingmuller, et al., Modulation of insulin-like growth factor-I production of cultured vascular endothelial cells by oxygen, glucose and growth hormone, Jpn. J. Ophthalmol. 46 (2002) 226–229.

[24] A. Hellstrom, C. Perruzzi, M. Ju, E. Engstrom, et al., Low IGF-I suppresses VEGF-survival signaling in retinal endothelial cells: direct correlation with clinical retinopathy of prematurity, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 5804–08.

[25] M.E. De Paepe, Q. Mao, J. Powell, et al., Growth of pulmonary microvasculature inventilated preterm infants, Am. J. Respir. Crit. Care Med. 173 (2006) 204–211.

[26] Hellström A, Ley D, Hansen-Pupp I, Hallberg B, Ramenghi L, Löfqvist C et al. IGF-I in the clinics: Use in retinopathy of prematurity. Growth Hormone & IGF Research. 2016;30-31:75-80.

[27] C. Lofqvist, E. Andersson, J. Sigurdsson, et al., Longitudinal postnatal weight and insulin-like growth factor I measurements in the prediction of retinopathy of prematurity, Arch. Ophthalmol. 124 (2006) 1711–18.

[28] Maggio M, De Vita F, Lauretani F, et al. IGF-1, the cross road of the nutritional, inflammatory and hormonal pathways to frailty. Nutrients 2013;5:4184–205.

[29] Can E, Bülbül A, Uslu S, Cömert S, Bolat F, Nuhoğlu A. Effects of aggressive parenteral nutrition on growth and clinical outcome in preterm infants. Pediatrics International. 2012;54(6):869-874.

[30] Hellstrom A, Hard A, Engstrom E, Niklasson A, Andersson E, Smith L et al. Early Weight Gain Predicts Retinopathy in Preterm Infants: New, Simple, Efficient Approach to Screening. PEDIATRICS. 2009;123(4):e638-e645.

[31] Embleton N. Optimal protein and energy intakes in preterm infants. Early Human Development. 2007;83(12):831-837.

[32] Vlaardingerbroek H, Vermeulen M, Rook D, van den Akker C, Dorst K, Wattimena J et al. Safety and Efficacy of Early Parenteral Lipid and High-Dose Amino Acid Administration to Very Low Birth Weight Infants. The Journal of Pediatrics. 2013;163(3):638-644.e5.

Table 1. Characteristics of Studies

Author	Sample	Types of Studies	Outcome	P value of ROP
Ming-Yi Liu et al (2015)	28 infants, 15 in conventional support group (CVS), 13 in aggressive support group (AGS) with a birth weight of <1500 g and more than 750 g were eligible for the study	Prospective Cohort Study	No difference in prevalence of ROP in groups receiving CVS and AGS	>0.05
Emrah can, et al 2013	Preterm infants <32 weeks, NGA 1:1 for conventional parenteral nutrition and aggressive parenteral nutrition 75 preterm infants	Prospective, randomized, double blind, clinical trial	ROP : 5% in APN group, 31.4% in CPN (5 with ROP stage 1), 6 in ROP stage 2) (p: 0.0004)	ROP incidence p value 0.004
Vanderveen et al (2013)	1180 infants, <28 weeks GA birth with ROP examination. Measured on postnatal days 3, 7, 14, and 21.	Prospective cohort study.		P value significant for infants whose recept of the fat, calories at p value= 0.05
Elisabeth Stoltz Sjöström et al (2015)	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.	A population-based cohort study	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	p value for fat is <0.001, p value for carbohydrate is < 0.01, p value for calories is < 0.001 while p value for protein is < 0.05

Table 2. Characteristics of Calories Used by Each Study

Author	Parameter Used	Conventional Parenteral Nutrition (CPN)	Aggressive Parenteral Nutrition (APN)	P Value of ROP
Ming-Yi Liu et al (2015)	kcal/kg/day	Week 1: 75.5 ± 11.2 Week 2: 81.6 ± 1.8 Week 3: 84.8 ± 11.0 Week 4 : 90.8 ± 13.3	Week 1 : 85.5 ± 8.4 Week 2 : 108.6 ± 13.1 Week 3 : 108.6 ± 14.4 Week 4 : 116.2 ± 14.4	0.047 <0.001 0.001 0.001
Emrah Can et al (2013)	Kcal/kg/day	115,5(28.5)	121,5 (35.5)	0.4
Vanderveen et al (2013)	kcal/kg/day	-	No ROP: 86 ROP: 78.7	<0.05
Elisabeth Stoltz Sjöström et al (2015)	Kcal/kg/day (10 kcal/kg/day increment)	Week 1-4: 102 (14)	Week 1: 66 (10) Week 2: 102 (17) Week 3: 116 (21) Week 4: 124 (21)	<0.01 <0.01 <0.001 <0.01

Table 3. Characteristics of Glucose Used by Each Study

Author	Glucose Used	Parameter Used	Conventional Parenteral Nutrition (CPN)	Aggressive Parenteral Nutrition (APN)	P Value of ROP
Ming-Yi Liu et al (2015)	Not Specified	g/kg/day	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	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	-
Emrah Can et al (2013)	Dextrose 2-%, 10% 5%, baxter/clintec, maurepance, france®	g/kg	-	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	>0.05
Vanderveen et al (2013)	Not Specified	g/kg/day		No ROP: 10 ROP: 7.53	<0.05
Elisabeth Stoltz Sjöström et al (2015)	Not Specified	g/kg/day (1 g/kg/day increment)	Week 1-4: 11.2 (1.1)	Week 1: 9.1 (1.3)	>0.05
				Week 2: 11.3 (1.4)	<0.05
				Week 3: 12.0 (1.6)	>0.05
				Week 4: 12.4 (1.7)	<0.05

Table 4. Characteristics of Lipid Used by Each Study

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

Table 5. Characteristics of Protein Used by Each Study

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