Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.64, No.4 (2024). p.318-24; DOI: https://doi.org/10.14238/pi64.4.2024.318-24

Original Article

The role of early aggressive nutrition on growth of very preterm or very low birth weight infants

Nadia Dwi Insani[1], Rinawati Rohsiswatmo[2], Damayanti Rusli Sjarif[2], Putri Maharani Tristanita Marsubrin[2], Klara Yuliarti[2], Lanny Christine Gultom[1]

Abstract

Background Very preterm infants (<32 weeks gestational age) are at high risk of poor neurodevelopmental outcomes. Early aggressive parenteral nutrition (protein ≥2g/kg BW/day) can reduce the incidence of malnutrition in very preterm infants. At present, Fatmawati General Hospital does not have a standard nutritional protocol for preterm infant.

Objective To determine the difference in growth (days to regain birth weight and growth velocity) of very preterm (<32 weeks gestational age) or very low birth weight (VLBW) (<1500g) infants who were born and hospitalized in the Neonatal Unit of Fatmawati General Hospital, Jakarta, before and after applying early aggressive parenteral nutrition using a nutrition protocol from Cipto Mangunkusumo Hospital, Jakarta.

Methods A quasi-experimental study was conducted on 23 very preterm or VLBW infants in the Neonatal Unit of Fatmawati General Hospital, from July to November 2019. Control group data were taken from medical records of very preterm or VLBW babies discharged from our unit from January 2018 to June 2019 and compared to those of the intervention group.

Results The intervention group regained their birth weight significantly faster than the control group [mean 7.43 (SD 3.5) *vs.* 16.73 (SD 5.1) days, respectively; (P=0.00)]. Mean growth velocity was also significantly higher in the intervention group than in the control group [14.6 (SD 6.0) *vs.* 8.9 (SD 6.9) gram/kg BW/day, respectively; (P=0.002)].

Conclusion Provision of early aggressive parenteral nutrition reduces the time to regain birth weight and leads to higher growth velocity in very preterm/VLBW infants. **[Paediatr Indones. 2024;64:318-24 DOI: https://doi.org/10.14238/pi64.4.2024.318-24**].

Keywords: *very preterm infant; very low birth weight; early aggressive parenteral nutrition; days to regain birth weight; growth velocity*

Premature infants are a high-risk group, vulnerable to poor neurodevelopmental outcomes.[1] Adequate growth and nutrition play an important role in improving long-term outcomes. Optimal nutrition affects brain development during fetal life and the first months after birth.[2] In the last decade, attention has focused on nutritional interventions that can improve the growth and development of premature infants. Nutrition for premature infants should result in growth rates similar to that of a fetus that grows normally at the same gestational age.[3] Unfortunately, most preterm infants are not adequately nourished to achieve this goal.[4] Early and aggressive feeding can reduce the incidence of extrauterine growth restriction (EUGR) in the postnatal period and improve long-term outcomes, particularly in maintaining the cognitive function of the brain.[5] Aggressive parenteral nutrition provides more energy and protein, leading to faster weight gain earlier discharge, and improved nutritional status upon discharge from NICU.[6]

From the Department of Child Health, Fatmawati General Hospital[1] and Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General Hospital[2], Jakarta, Indonesia.

Corresponding author: Nadia Dwi Insani. Department of Child Health, Neonatal Unit - Fatmawati General Hospital. Jl. RS Fatmawati, Cilandak, Jakarta Selatan, Indonesia. Email: nadiainsani@gmail.com.

Submitted September 22, 2023. Accepted August 30, 2024.

Nutritional protocols for very premature infants vary among neonatal intensive care units (NICU) in Indonesia. Some protocols introduce parenteral nutrition slowly during the first week, due to concerns of complications such as metabolic acidosis or worsening sepsis. It is often accepted that periods of nutritional deficiency are common and difficult to avoid in this population. Nutritional strategies that are too careful can cause early malnutrition and prolonged recovery periods in very premature infants, and put them at risk of long-term complications.[7] Avoiding EUGR has both short- and long-term benefits for preterm infants. This strategy involves giving early aggressive parenteral nutrition and enteral feeding as soon as the infant is stable.[8] Parenteral nutrition is often used to achieve minimum nutritional requirements in the first days of life of very premature or VLBW infants, gradually working up to full enteral feeds.

Currently, most hospitals in Indonesia do not have standardized nutritional protocols to care for very premature babies. Often the amounts of calories, protein, and fat are given slowly and do not meet the high needs of very premature or VLBW infants early in life. At our unit, most very premature or VLBW infants receive parenteral protein on day 3, increasing gradually from 1-3g/kg BW/day. Lipids are not routinely administered. Since 2016, Cipto Mangunkusumo General Hospital, Jakarta, the national reference hospital in Indonesia, has given early aggressive nutrition from the first day of life (protein 2.5g/kg/day) for very or extremely premature infants.[9,10] Fatmawati General Hospital, Jakarta, one of their network hospitals, aims to improve in the provision of nutrition for our very premature and VLBW infants by implementing the Cipto Mangunkusumo General Hospital protocol. Our goal was to reduce the time to regain birth weight and increase the growth velocity of VLBW or very premature infants born in Fatmawati Hospital. Hence, we performed this study to compare these two variables in infants who received early aggressive parenteral nutrition and a control group who received nutrition using a conservative protocol.

Methods

This quasi-experimental study was conducted in the Neonatal Unit of Fatmawati Hospital. Intervention with early aggressive parenteral nutrition was carried out from July to November 2019. The study population was very premature infants (<32 weeks gestational age) or VLBW infants born and hospitalized in the Neonatal Unit of Fatmawati General Hospital. Infants in the intervention group were included consecutively until the minimum sample size was met. Infants in the control group were included based on medical record data of very premature or VLBW infants in the period before intervention (January 2018 - June 2019). The required minimum sample size was calculated from a formula to estimate the mean difference between two populations and determined to be 23 per group.

Exclusion criteria were infants whose parents refused to participate in the study, had congenital/gastrointestinal disorders that affected nutritional status, or had incomplete medical records of daily weight (for the control group). Subjects' parents provided written informed consent before intervention. The total parenteral nutrition (TPN) unit of the hospital provided the sterile parenteral nutrition fluids for subjects.. Subjects in the intervention group received early aggressive parenteral nutrition, starting with protein at 2.5g/kg/day and lipids at 1g/kg/day from the first day, increasing gradually according to the Cipto Mangunkusumo nutrition protocol (**Table 1**).[9] The nutrition for the control group has no standard protocol, however they received in general a calorie of 50 calorie/kg/day and a protein of 2 g/kg/day.

Days to regain birthweight and growth velocity were recorded to evaluate growth. Growth velocity was calculated from the day infants regained their birth weight and calculated at discharge or death. Dependent variables were number of days to regain birth weight and growth velocity at discharge or death. Secondary outcomes were time starting enteral feed, time to full feed, time of protein and lipid administration, time to achieve highest protein, lipid, and calories (in days), as well as the highest amounts of protein, lipid, calories, and glucose infusion rate (GIR) given. The incidences of respiratory distress syndrome, neonatal sepsis, and necrotizing enterocolitis in both groups was recorded and analyzed. Data were compared between the two groups using T-test for independent groups.

Table 1. Dr. Cipto Mangunkusumo Hospital neonatal parenteral nutrition protocol[9]

Days	Fluid, mL/kg	GIR, mg/kg BW/min	Protein, g/kg	Lipid, g/kg	
	Birthweight < 1,000g or GA < 28 wks			< 700gr	>700-999 gr
0	80	6-8	2.5	0.5	1
1	100	7-8	3	1	1.5
2	120	8-9	3.5	1.5	2
3	140	9-10	3.5	2	2.5
4	150	10-11	3.5	2.5	3
5	150	11-12	3.5	3	3
	Birthweight 1,000-1,499 g or GA 28-32 wks				
0	80	6-8	2.5	1	
1	100	7-8	3	2	
2	120	8-9	3.5	3	
3	140	9-10	3.5	3	
4	150	10-11	3.5	3	
5	150	11-12	3.5	3	
	Birthweight 1,500-2,499 g or GA 33 - < 37 wks				
0	60	4-6	0	0	
1	80	6-8	1.5	1	
2	100	8-9	2.5	2	
3	120	9-10	3	3	
4	140	10-11	3	3	
5	150	11-12	3	3	
	Birthweight ≥2,500 g or GA 37-42 wks				
0	60	4-6	0	0	
1	80	6-8	0	0	
2	100	8-9	1	1	
3	120	9-10	2	2	
4	140	10-11	3	3	
5	150	11-12	3	3	

Results

Infants were included consecutively from July to November 2019. Fifty-seven infants were screened for the control group, but 34 had incomplete medical record data. Thirty infants in the intervention group met the inclusion criteria, but 7 died before 14 days. Twenty-three infants received early aggressive parenteral nutrition.

The result of the univariate test for subjects' characteristics is shown in **Table 2**. The table shows that the characteristics of the control and treatment group had no significant differences. The characteristics chosen for this study were birth weight, gestational age, respiratory distress syndrome, neonatal sepsis, and necrotizing enterocolitis. Since there were no significant differences for the chosen characteristics between the two groups, any difference in outcomes were attributed to the treatment. The data in **Table 2** were taken before the intervention. **Table 3** shows that all variables were significantly higher in the intervention group than in the control group (P=0.001 for all). **Table 4** shows that the mean time to regain birthweight was significantly shorter (7.4 days) for the intervention group compared to the control group (16.7 days). The intervention group also showed a significant higher growth velocity (14.6) compared to the control group (8.9).

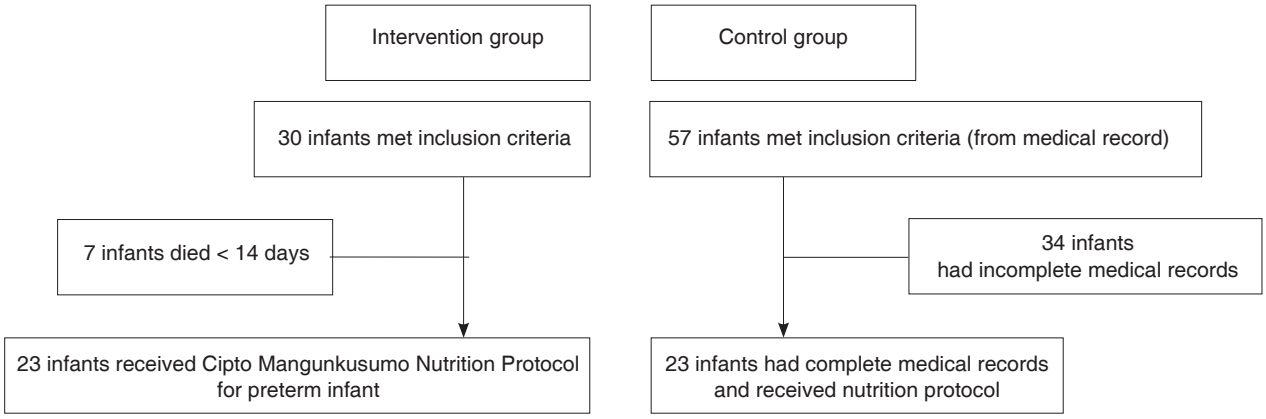

Figure 1. Participant selection flowchart

Table 2. Characteristics of subjects

Characteristics	Control group (n=23)	Intervention group (n=23)	P value
Mean birth weight (SD), g	1,294 (172)	1,356 (169)	0.115
Mean gestational age (SD), weeks	31.2 (2.6)	31.3 (2.0)	0.463
Appropriate for gestational age, n	16	15	0.753
Small for gestational age, n	7	8	0.753
Respiratory distress syndrome, n	14	14	1.000
Neonatal sepsis, n	13	10	0.376
Necrotizing enterocolitis, n	3	3	1.000

Table 3. Highest amount of given protein, calorie and glucose infusion rate (GIR)

Provision pattern of nutrition	Control group (n=23)	Intervention group (n=23)	P value
Mean highest amount of protein (SD), g/kg/day	2.8 (0.5)	3.2 (0.4)	0.001
Mean highest amount of calories (SD), cal/kg/day	48.4(13.2)	100.7(7.5)	0.001
Mean highest amount of GIR (SD), mg/kg/min	5.7 (3.1)	10.7 (1.2)	0.001

Table 4. Analysis of time to regain birthweight and growth velocity

Variables	Control group (n=23)	Intervention group (n=23)	P value
Mean time to regain birthweight (SD), days	16.7 (5.1)	7.4 (3.5)	0.000
Mean growth velocity (SD), g/kg/day	8.9 (6.9)	14.6 (6.0)	0.002

Discussion

Beyond the differences in nutrition given to the two groups, other factors thought to affect the nutritional status of premature infants, such as gestational age, birth weight and the occurrence of several diseases or complications were not significantly different in the two groups. Thus, we concluded that nutritional interventions of the two groups was the primary difference leading to growth outcomes.

In our study, the mean time to regain birth weight was significantly faster in the intervention group than in the control group [7.4 (3.5) *vs.* 16.7 (5.1) days, respectively; P=0.001]. Newborns are expected to regain birth weight by 7-14 days of age, although not all do. Optimal fluid and nutritional management can

reduce the duration of weight loss and prevent slow growth after birth. Postnatal weight loss can be due to inadequate nutrition, and time taken to regain birth weight can be used as a parameter to assess hospital malnutrition.[10] Our finding was consistent with a study that compared two similar groups, which one group was given low-dose parenteral nutrition/LPDN (control group) and the other was given high-dose parenteral nutrition/HPDN (intervention). The study also found that a higher amount of protein shortens the days to regain birth weight (13 (LPDN) *vs.* 9.6 (HPDN) days; P=0.001).[11]

Growth velocity can be used to monitor infant growth after infants regain their birth weight. The growth rate of premature infants is expected to be similar to that of fetuses. A previous study concluded that a growth rate of 15-20g /kg/ day (using the average or exponential method) is an acceptable target for growth in infants with 23-36 weeks gestational age, but not in infants with older gestational age because human growth is not constant during different gestational periods.[12] We evaluated growth velocity in both treatment groups. Although neither group achieved the growth velocity as expected (15g/kg/day), that of the intervention group was significantly higher than in the control group [14.6 (SD 6.0) *vs.* 8.8 (SD 6.8) g/kg/day, respectively; P=0.002].

The basic principle of early aggressive nutrition is to provide high amounts of protein early in life. This is important to prevent EUGR in very premature infants. A very premature infant loses 1-2% or 0.6-1.2 g/kg BW/day of protein if their only source of calories comes from carbohydrates. Protein loss increases with advancing gestational age.[13] Protein deficits in preterm infants lead to long- and short-term morbidity. The pursuit of growth takes a long time and nutritional deficiencies at the time of birth impacts developmental and cognitive impairments, comparable to growth disorders.[2,4] Providing more than 2g/kg BW/day of amino acids from the first day of life prevents protein catabolism and negative nitrogen balance, induces positive nitrogen balance, and promotes body weight and growth.[5] Such aggressive administration also increases endogenous insulin secretion and gluconeogenesis, thereby increasing glucose tolerance and preventing hyperglycemia.[5] In our study, the amount of protein given was higher in the intervention group than that given to the control group [3.2 (SD 0.4) *vs.* 2.8 (SD 0.5) gram/kg BW/day, respectively; P=0.001] and no side effects were seen.

Fat is also an important component of parenteral nutrition for premature infants. Fat reserves in the infant's body are the largest energy reserves at birth.[3] VLBW and extremely low birth weight (ELBW) infants have very limited fat reserves, so they are very dependent on enteral and parenteral nutrition. The available evidence suggests that the application of lipids in the early stages of life determines a variety of outcomes, including physical growth and intellectual development. Rapid brain growth early in life makes premature infants particularly vulnerable to nutritional deficits. The neurological development of premature VLBW infants requires early lipid supplementation.[14] Early administration can increase energy intake, providing essential fatty acids and fat-soluble vitamins.[15] The Cipto Mangunkusumo protocol recommends that lipids be given in the first 24 hours. But in our hospital, lipids are not given routinely. Lipid administration was found in only 5 infants from the control group.

Finally, regarding the significant difference in growth, we found that the highest administration rate of calorie and GIR were significantly higher in the intervention compared to the control group [calorie: 100.7 (SD 7.5) *vs.* 48.4 (SD 13.2) cal/kg BW/day, respectively; P=0.001; GIR 10.7(SD 1.2) *vs.* 5.7(SD 3.1) g/kg BW/day, respectively; P=0.001]. Preterm infants require high protein and calories to mimic an intrauterine growth similar to the condition in pregnancy. Once protein intake is sufficient to promote muscle mass growth, the energy boost primarily results in more body fat, which increases almost linearly at an energy intake of 90-100 kcal/kg BW/day while the infant receives parenteral nutrition. Glucose administration is expected to start with GIR 6-8 mg/kg BW/minute, gradually increasing by 1-2 mg/kg BW/minute until it reaches a maximum at 11-12 mg /kg BW/minute.[8]

Giving high protein without adequate calories results in conversion of protein into energy and not into lean body mass. This will lead to poor weight gain, especially if enteral feeding cannot be rapidly increased. Adequate provision of protein and energy in the first week was associated with a higher Mental Development Index score in LBW infants at 18 months of age.[2] In our unit, growth of very premature

or VLBW infants was slow because of the inadequacy of the parenteral regimen, and no standard protocol had been used for providing early aggressive nutrition.

The limitation of this study was the use of historical data for the control group. We could not perform a randomized controlled trial because it is considered unethical to provide ideal nutrition to only the intervention group. We also did not include phosphate in our TPN regimen because a phosphate-containing parenteral regimen was not yet available in Indonesia.

In conclusion, our findings suggest that the provision of high calorie and early aggressive nutrition using a standard nutrition protocol can accelerate the time to regain birth weight and growth velocity in very preterm or very low birth weight infants. It is important to give high amounts of non-protein calories and early aggressive parenteral nutrition to very premature or VLBW infant to promote normal growth rate and hasten the time for discharge.

Conflict of interest

None declared.

Acknowledgement

We would like to thank the Pharmacy Unit of Cipto Mangunkusumo and Fatmawati General Hospital for their full support in the implementation of this study.

Funding acknowledgement

The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Sices L, Wilson-Costello D, Minich N, Friedman H, Hack M. Postdischarge growth failure among extremely low birth weight infants: correlates and consequences. Paediatr Child Health. 2007;12:22-8. PMID: 19030335.
2. Stephens BE, Walden R V, Gargus RA, Tucker R, McKinley L, Mance M, *et al.* First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. Pediatrics. 2009;123:1337-43. DOI: https://doi.org/10.1542/peds.2008-0211
3. Su B-H. Optimizing nutrition in preterm infants. Pediatr Neonatol. 2014;55:5-13. https://doi.org/10.1016/j.pedneo.2013.07.003
4. Thureen PJ, Hay WW Jr. Early aggressive nutrition in preterm infants. Semin Neonatol. 2001;6:403-15. DOI: https://doi.org/10.1053/siny.2001.0061
5. Hay Jr WW, Brown LD, Denne SC. Energy requirements, protein-energy metabolism and balance, and carbohydrates in preterm infants. World Rev Nutr Diet. 2014;110:64-81. DOI: https://doi.org/10.1159/000358459
6. Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. Pediatrics. 2003;111:986-90. DOI: https://doi.org/10.1542/peds.111.5.986
7. Ruth VA. Extrauterine growth restriction: a review of the literature. Neonatal Netw. 2008;27:177-84. DOI: https://doi.org/10.1891/0730-0832.27.3.177
8. Ikatan Dokter Anak Indonesia. Konsensus asuhan nutrisi pada bayi prematur. Jakarta: BP IDAI: 2016.
9. Sjarif DR, Rohsiswatmo R, Rundjan L, Yulianti K. Panduan berbasis bukti asuhan nutrisi untuk bayi prematur. EC000202061182. 2020.
9. Ikatan Dokter Anak Indonesia. Kadim M, Roeslani R, Nurmalia L, eds. Konsensus asuhan nutrisi pada bayi prematur. Jakarta: Badan Penerbit IDAI; 2016.
10. Goldberg DL, Becker PJ, Brigham K, Carlson S, Fleck L, Gollins L, *et al.* Identifying malnutrition in preterm and neonatal populations: recommended indicators. J Acad Nutr Diet. 2018;118:1571-82. DOI: https://doi.org/10.1016/j.jand.2017.10.006
11. Törer B, Hanta D, Özdemir Z, Çetinkaya B, Gülcan H. An aggressive parenteral nutrition protocol improves growth in preterm infants. Turk J Pediatr. 2015;57:236-41. PMID: 26701941.
12. Fenton TR, Anderson D, Groh-Wargo S, Hoyos A, Ehrenkranz RA, Senterre T. An attempt to standardize the calculation of growth velocity of preterm infants - evaluation of practical bedside methods. J Pediatr. 2018;196:77-83. DOI: https://doi.org/10.1016/j.jpeds.2017.10.005
13. Ziegler EE, Carlson SJ. Growth failure due to inadequate protein intake is common among small preterm infants. Nutr Today. 2016;51:228-32. DOI: https://doi.org/10.1097/NT.0000000000000172
14. dit Trolli SE, Kermorvant-Duchemin E, Huon C, Bremond-

Gignac D, Lapillonne A. Early lipid supply and neurological development at one year in very low birth weight (VLBW) preterm infants. Early Hum Dev. 2012;88:S25-9. DOI: https://doi.org/10.1016/j.earlhumdev.2011.12.024

15. Vlaardingerbroek H, Veldhorst MAB, Spronk S, van den Akker CHP, van Goudoever JB. Parenteral lipid administration to very-low-birth-weight infants - early introduction of lipids and use of new lipid emulsions: a systematic review and meta-analysis. Am J Clin Nutr. 2012;96:255-68. DOI: https://doi.org/10.3945/ajcn.112.040717
16. Embleton ND. Optimal protein and energy intakes in preterm infants. Early Hum Dev. 2007;83:831-7. DOI: https://doi.org/10.1016/j.earlhumdev.2007.10.001