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Original Article

Paediatrics Section

Safety and Outcome of High Dose Parenteral Amino Acid Supplementation for VLBW Neonates on Partial Parenteral Nutrition: A Randomised Controlled Study

RAKESH GAMI, MANISHA BHANDANKAR

ABSTRACT

Introduction: Total Parenteral Nutrition (TPN) is prescribed to meet a neonate's requirement for growth and development when his/her condition and/or gestation prevents complete enteral feeding. In India Partial Parenteral Nutrition (PPN) is used in neonatal units with inadequate facilities to prepare TPN.

Aim: To evaluate the effect of supplementation of high dose parenteral Amino Acid (AA) on growth and biochemical parameters of Very Low Birth Weight (VLBW) neonates receiving PPN in first week of life.

Materials and Methods: This was a Randomised controlled study, conducted in a tertiary care medical center. Sixty VLBW newborns with birth weight of <1500 gm admitted to level III NICU within 24 hour of life were included and Randomised into two groups of AA supplementation: One group received 1 g/kg/day of parenteral AA (Aminoven) on day 1, which was increased by 1g/kg/day till 4 gm/kg/day. The other group received 3 g/kg/day of parenteral AA on day 1, which was increased to 4 g/kg/day on the next day. Both the groups were continued on AA till they reached 75% of enteral feeds. Independent sample and chi-square test were used to analyse the data.

Results: With similar baseline characteristics, serum sodium ($p = 0.001$) and blood urea ($p = 0.041$) levels were higher during 1st week of hospital stay. The daily physiological weight loss was more in neonates who received high AA from day 1 of life. There was no significant difference in weight gain ($p>0.05$) between the two groups during the hospital stay. The mean hospital stay was 23±4.5 days for Group A and 22.4± 3.6 days for Group B.

Conclusion: Supplementation of high dose parenteral AA in VLBW infants receiving PPN does not help in weight gain during hospital stay, although well tolerated.

Keywords: Birth weight, Blood urea nitrogen, Sodium, Tertiary healthcare, Weight gain, Weight loss

INTRODUCTION

The VLBW infants (weighing <1.5 kg) are vulnerable to increased mortality and morbidity during neonatal period, infancy, and childhood due to susceptibility to infections, early growth retardation, and developmental delay [1]. VLBW neonate could be born preterm, small size for gestational age, or sometimes both.

TPN is a delivery of nutrition through parenteral route for growth and metabolic requirements. TPN is prescribed to meet a neonate's requirement for growth and development when his/her condition and/or gestation prevents complete enteral feeding. Although, early aggressive enteral nutrition is recommended in VLBW neonates, need for high ventilator settings, ionotropic support, immature gastrointestinal system, surgery, and infection are some of the main factors that lead to withholding of enteral feeding in first few days of life [2]. In India, use of TPN solutions have improved substantially since the early days and complications are now less common due to the administration of amino acids (AAs) and lipids in the Neonatal Intensive Care Unit (NICU) [3,4]. However, the use of TPN is still influenced by affordability of parents, availability of trained nursing staff, and willingness of the neonatologist to prescribe it [3,4].

Premature VLBW neonates are devoid of fetal accretion of nutrients in last trimester leading to limited glycogen and fat reserve and have slow postnatal weight gain. Postnatal growth of VLBW neonates has remained a major challenge in the NICU [5]. There is enough evidence to support that administration of early and aggressive parenteral nutrition and enteral nutrition is beneficial [6,7]. Administration of high dose

AAs, from day 1, in VLBW neonates have resulted in better plasma AA profile and nitrogen accretion and are well tolerated. However, its role in improving postnatal growth rate and long-term neurodevelopment is still not clear [8-12]. In India, due to resource-limited settings, the use of micronutrients and lipids is restricted in parenteral nutrition [13]. Hence, PPN comprising of glucose, AAs, and electrolytes without lipids is prescribed to the preterm neonates. The role of clinical pharmacist is limited and most of the units prepare their parenteral nutrition by training the nursing staff. Parenteral nutrition can be used only if trained nursing staff are available, who can prepare and administer PN with proper aseptic precautions and if facilities are available for monitoring biochemical parameters regularly.

Postnatal growth restriction in preterm infants is mainly due to a low caloric intake during the first few weeks of life [14,15]. Randomised controlled studies are conducted which reported that early AA supplementation (starting within few hours of birth) as compared to AA supplementation after 3-5 days of life resulted in better postnatal growth in preterm LBW neonates [13,16,17]. Early administration of AA can promote anabolism through positive nitrogen balance [14,15]. In recent times, it has become evident that protein delivery of 3 g/kg/day beginning on day one of life is safe and associated with plasma AA concentration similar to those of second and third trimester fetuses. However, most of these studies were performed in neonates who received TPN [7]. Therefore, we undertook this study to evaluate the safety of administering a higher dose (3 g/kg/day) from day 1 of life in comparison to gradual increments in dose of parenteral AAs in the PPN regimen and its effect on weight loss in the first week of life. The primary outcome measured safety. Secondary outcomes measured growth parameters (weight, length, and head circumference) and biochemical variables (sodium, potassium, blood urea, serum calcium, blood urea nitrogen).

MATERIALS AND METHODS

The Randomised controlled study was conducted from January 2015 to February 2016 at level III NICU, Department of Paediatrics, KLE University's Jawaharlal Nehru Medical College, Belgaum Karnataka, India. All out born and inborn neonates weighing <1500 g admitted within 24 hours of life in NICU were included. Neonates with congenital anomalies or inborn errors of metabolism (IEM), needing surgery, discharged as AMA, and death during NICU stay were excluded from study. A written consent was obtained from the parents/caregivers before enrolment. The study was approved by the Institutional Ethics Committee.The sample size was calculated based on the following formula.

$$n = \frac{2(Z_\alpha + Z_\beta)^2 (S_1^2 + S_2^2)}{(n_1^2 + n_2^2)}$$

$$n = \frac{2(1.96+0.84)^2 * (5^2+4^2)}{(13-9)^2} = 26$$

Where, Zα = type 1 error =1.96; Zβ= type 2 error = 0.84; S1= 5; S2= 4; n^1 = 13; n^2= 9

Considering power of the study as 80%, the sample size per group was 26. Total sample size including 10% drop out. Hence, the sample size of 30 was included per each group.

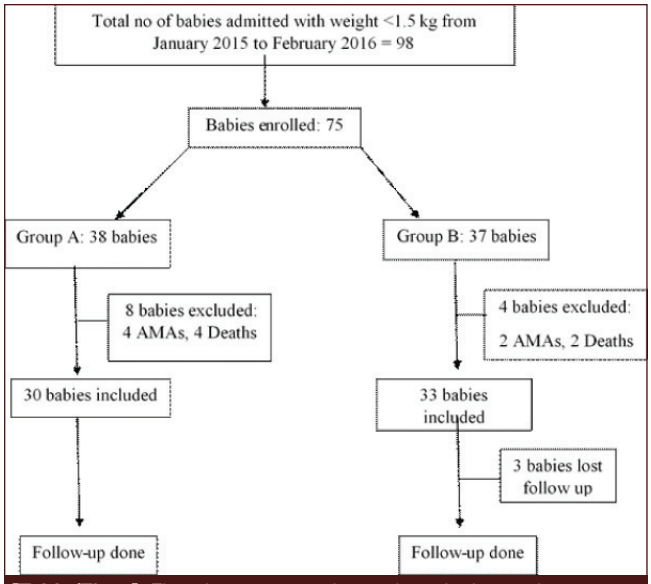
This NICU followed the protocol of starting AA at 1 g/kg/day from day one. During the study, neonates were Randomised into two groups. Group A and Group B by on-duty postgraduate with odd and even numbers to receive two different doses of parenteral AA preparation. On day one, PPN was administered to the neonates in both groups, which composed of dextrose (glucose infusion rate (GIR) 6-8 mg/kg/min), AAs, calcium, and multivitamin (1 ml/kg) either through peripheral line or Peripherally Inserted Intravenous Catheter (PICC) line. Group A received 1 g/kg/day of parenteral AA on day one and dose was increased by 1 gm/kg/day every day till maximum of 4 gm/kg/day. Group B received 3 gm/kg/day of parenteral AA on day one and dose was increased to 4 gm/kg/day on next day. Total fluids were calculated as per the standard recommendations (80 mL/kg on day 1, increased gradually to maximum 150 mL/kg). Rest of the care in both the groups was provided as per standard neonatal practices, including ventilation, use of antibiotics, and Kangaroo mother care [16]. Trophic feeding was started within 48 hour of life, except where contraindicated and increased as per the unit protocols and as tolerated by the preterm infants till 130-150 mL/kg. Trophic feeds were given once the baby was stabilized after birth and gradually increased everyday i.e., 10-15 mL/kg/day till baby reached full target feeds of 140 mL/kg/day. The follow-up was done and data was collected till 40th week [16]. Both groups were continued on AA till they reached 75% of enteral feeds. Weight, length, and head circumference were measured at admission and every week during hospital stay. Biochemical parameters, including serum sodium, serum potassium, serum calcium, blood urea, and total calcium were monitored weekly during hospital stay.

STATISTICAL ANALYSIS

The data were analysed using SPSS 20.0 statistical software. Continuous data were expressed as mean ± standard deviation (SD). Independent sample t-test was used to assess the significance of study parameters on continuous scale between two groups. Chi-square test was used to find association between the classes of variables. A p-value ≤0.05 at 95% confidence interval (CI) was considered as statistically significant.

RESULTS

Between January 2015, and February 2016, although 98 VLBW neonates admitted, 60 neonates completed follow-up after discharge at 40 weeks, hence only 60 were included with 30 in each group [Table/Fig-1].



[Table/Fig-1]: Flowchart representing patients in the study.

Demographic data and clinical characteristics

The demographic and clinical characteristics of the neonates are shown in the [Table/Fig-2]. No significant difference was observed in gender, gestational age, mode of delivery, birth weight, and characteristics of study population between the two groups. Three neonates in group B weighed <1000 g. The mean hospital stay was 23±4.5 days for Group A and 22.4±3.6 days for Group B.

Anthropometric measurements

Changes in the mean weight of the neonates in both groups at weekly intervals was not significantly different as shown in the [Table/Fig-3]. Similarly, the changes in head circumference and length were comparable. [Table/Fig-4] shows the mean daily weight change in both the groups. Interestingly the daily weight loss in group B was significantly more than that in group A in the first week of life. However, during the rest of the hospital stay, the daily weight gain was more in this group of neonates. There were three neonates with birth weight <1000 g in group B. This could have affected the change in mean weight that is observed in group B.

Biochemical profile

The mean sodium, potassium, blood urea, serum calcium, and blood urea levels from first week to fourth week are shown in

Variable	Group A (n=30)	Group B (n=30)	p-value
Gender			
Male	16 (53.33%)	14 (46.67%)	0.606
Female	14 (46.67%)	16 (53.33%)	
Gestational age (weeks)			
28 weeks-31 week 6 days	9 (30%)	10 (33.33%)	0.824
32 weeks-36 week 6 days	19 (63.33%)	19 (63.33%)	
37 weeks-39 week 6 days	2 (6.67%)	1 (3.34 %)	
Mode of delivery			
Caesarean	25 (83.33%)	24 (80%)	0.739
Vaginal	5 (16.67%)	6 (20%)	
Birth weight (gm)			
<1000	0	3 (10%)	0.237
1000–1500	30 (100%)	27 (90%)	
Characteristics of study population			
Gestational age (week)	32±2.32	32.90±2.10	>0.050
Birth weight (gm)	1351.67±124.40	1326.93±189.11	
Head circumference at the time of admission (cm)	28.57±1.25	28.40±1.43	
Length at the time of admission (cm)	37.70±2.60	39.15±3.27	

[Table/Fig-2]: Demographic and baseline characteristics of neonates.

Interval (week)	Weight (g)		Head circumference (cm)		Length (cm)	
	Group A	Group B	Group A	Group B	Group A	Group B
1	1331.60±131.45^{ns}	1297.50±179.92^{ns}	28.60±1.16^{ns}	28.37±1.40^{ns}	37.55±2.86^{ns}	38.82±2.89^{ns}
2	1330.46±162.71^{ns}	1242.90±194.40^{ns}	28.61±1.10^{ns}	28.45±1.38^{ns}	37.61±2.91^{ns}	39.03±2.77^{ns}
3	1324.93±185.53^{ns}	1262.1±217.4^{ns}	29.10±1.39^{ns}	28.60±1.50^{ns}	37.73±3.22^{ns}	38±2.33^{ns}
4	1270±151^{ns}	1205.75±214.19^{ns}	28.86±1.07^{ns}	27.88±1.13^{ns}	37.29±3.15^{ns}	38.63±2.56^{ns}

[Table/Fig-3]: Comparison of anthropometric measurements in neonates at weekly intervals.
ns: p> 0.05; s: p< 0.05

Interval	Number of babies	Group A (Mean±SD)	Number of babies	Group B (Mean±SD)	p-value
Birth to week 1	30	-2.87±9.91	30	-4.20±7.73	0.012
Week 1 to week 2	28	1.35±10.48	29	3.81±9.10	0.047
Week 2 to week 3	15	7.29±8.45	15	9.04±4.11	0.012

[Table/Fig-4]: Comparison of change in weight per day during hospital stay.

Variables	1st week		2nd week		3rd week		4th week	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
Sodium (meq/L)	131.17±3.66^{S}	140.5±3.15^{S}	135.3±3.15^{ns}	135.8±4.38^{ns}	133.7±5.40^{ns}	133.5±3.71^{ns}	133.3±8.08^{ns}	136.20±6.87^{ns}
Potassium (meq/L)	4.89±0.84^{ns}	4.92±0.83^{ns}	4.67±0.64^{ns}	5.12±0.89^{ns}	4.52±0.34	4.75±0.56^{ns}	4.30±0.53^{ns}	4.42±0.69^{ns}
Blood urea (mg/dL)	25.79±14.86^{s}	32.31±8.26^{s}	36.46±22.3^{ns}	33.59±19.3^{ns}	39.91±27.84	26.20±11.44^{ns}	19.40±4.50^{ns}	21.04±8.63^{ns}
Serum calcium (mg/dL)	8.56±0.66^{ns}	8.66±0.77^{ns}	9.07±0.52^{ns}	9.13±0.88^{ns}	9.20±0.49	9.19±0.5^{ns}	8.90±0.17^{ns}	9.08±0.70^{ns}
Blood urea nitrogen (mg/dL)	12.04±6.94^{S}	15.08±3.86^{S}	17.02±10.41^{ns}	15.67±9.01^{ns}	18.63±12.99^{ns}	12.33±5.34^{ns}	9.05±2.10^{ns}	9.82±4.03^{ns}

[Table/Fig-5]: Comparison of biochemical parameters.
ns: p >0.05; s: p <0.05

the [Table/Fig-5]. Although, mean values of sodium ($p<0.001$), blood urea ($p=0.041$), and Blood Urea Nitrogen (BUN) showed statistically significant difference in both groups, they were within normal range. Rest of the biochemical parameters were comparable. However, weekly monitoring of these parameters during rest of the hospital stay were comparable between the two groups.

DISCUSSION

It was found that PPN consisting of 3 g/kg/day of parenteral AA on day 1 and increased to 4 g/kg/day is well-tolerated by VLBW neonates than the gradual increments in parenteral amino acid supplementation (i.e., 1g/kg/d on day 1 of life).

In TPN, the ratio of protein: nonprotein caloric intake is important to prevent oxidation of AAs [3]. In this study, parenteral lipids were not used due to resource limitations. Maximum Glucose infusion rate was 12 mg/kg/hour to maintain blood glucose level between 80-120 mg/dL. This did not improve the ratio of non-protein caloric intake to calories from protein to the desired level of 100-200 Cal/g of protein needed for adequate postnatal growth. VLBW neonates who receive only glucose can have protein loss of 0.5-1 g/kg/day. It has been shown that early administration of AA may in fact lead to decreased glucose levels due to stimulation of insulin secretion [13].

Although, the neonates received higher amounts of protein in group B as compared to group A, it was not used for growth and accretion of protein. Studies in preterm neonates suggest that the effect of AA intake on protein accretion occurs through increased protein synthesis rather than inhibition of protein breakdown [7]. A study conducted by Denne SC et al., demonstrated an increase in protein synthesis with PN [18]; however, there was significantly less suppression of protein

breakdown in the preterm neonates. Further, the mechanism of action by which AA intake promotes protein accretion in neonates is not clearly reported [7]. Balasubramanian H et al., reported that 1 g/kg/ day of parenteral AAs on day 1 with gradual increments of 1 g/ kg/day till a maximum of 4 g/kg/day resulted in better growth (weight, length, and head circumference) than early aggressive parenteral AA supplementation (3 g/kg on day 1 of life) in VLBW neonates [13]. Randomised controlled trial (RCT) conducted by Bulbul A et al., reported no significant difference in body weight and head circumference in the high versus low AA group during first 2 weeks [8].

The BUN levels, although within normal range, were found to be higher in group B compared to group A in the first week (15.08±3.86 vs. 12.04±6.94 mg/dL; $p<0.001$). At second, third, and fourth week, BUN levels were not statistically significant in both the groups ($p>0.050$). Many studies have shown no relationship between BUN and AA intake [9,11,13,17]. Aggressive PN has been shown to be well tolerated with no adverse clinical and biochemical outcomes [9,10,19].

High dose AA intake may result in hypokalemia and hypophosphatemia due to accelerated protein synthesis. This may lead to increased plasma calcium concentration as a result of mobilization of endogenous phosphates if they are not supplied adequately [20]. In our study although the difference in protein supplementation was for first four days, we assessed the levels of plasma calcium concentration, which were comparable throughout the hospital stay in both the groups.

The administration of parenteral AA along with lipids from day 1 of birth has shown to improve conditions for anabolism as well as growth in VLBW neonates. Greater levels of AA administration do not further improve the nitrogen balance but lead to increased AA oxidation. This study has also shown that early high AA dose was well tolerated in VLBW neonates, however, did not lead to increase in protein synthesis and anabolism.

The time taken to reach full enteral feeds was not studied during this study. It has been reported that neonates who receive lesser AA in first week of life take longer time to reach full enteral feeds compared to those who receive high AA supplementation [11]. The duration of hospital stays, and other co-morbidities did not vary significantly between the two groups.

LIMITATION

The small sample size is a main drawback to determine the significance of administering high AA dose (3 g/kg/day) from day 1 of life on growth of preterm VLBW neonates who do not receive parenteral lipids. Use of TPN may show different study outcomes in terms of postnatal growth.

CONCLUSION

Overall, the study showed that PPN consisting of 3 g/kg/day of parenteral AA on day 1 and increased to 4 g/kg/day on next day is well tolerated by VLBW neonates. To ensure adequate postnatal growth, it is essential to use TPN from day 1 of life for very and extreme low birth weight neonates. Administration of high dose of AA with PPN does not serve the purpose of protein anabolism and growth of the baby.

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REFERENCES

[1] World Health Organization. Feeding of very-low-birth-weight infants. Geneva: WHO, 22-11-2018. (Available from: http://www.who.int/elena/titles/feeding_vlbw_infants/en/).
[2] Ehrenkranz RA. Early, aggressive nutritional management for very low birth weight infants: What is the evidence? Semin Perinatol. 2007;31:48-55.
[3] Chaudhari S, Kadam S. Total parenteral nutrition in neonates. Indian Pediatr. 2006;43:953.
[4] Chaudhari S, Vaidya UV. Total parenteral nutrition in India. Indian J Pediatr.1988;55:935-40.
[5] Ziegler E, O'donnell A, Nelson S, Fomon S. Body composition of the reference fetus. Growth. 1976;40:329-41.
[6] Ibrahim HM, Jeroudi MA, Baier R, Dhanireddy R, Krouskop RW. Aggressive early total parental nutrition in low-birth-weight infants. J Perinatol. 2004;24:482.
[7] Thureen PJ, Melara D, Fennessey PV, Hay WW. Effect of low versus high intravenous amino acid intake on very low birth weight infants in the early neonatal period. Pediatr Res. 2003;53:24-32.
[8] Bulbul A, Okan F, Bulbul L, Nuhoglu A. Effect of low versus high early parenteral nutrition on plasma amino acid profiles in very low birth-weight infants. J Matern Fetal Neonatal Med.2012;25:770-76.
[9] Osborn DA, Schindler T, Jones LJ, Sinn JK, Bolisetty S. Higher versus lower amino acid intake in parenteral nutrition for newborn infants. The Cochrane Library. 2018.
[10] Bonsante F, Gouyon J-B, Robillard P-Y, Gouyon B, Iacobelli S. Early optimal parenteral nutrition and metabolic acidosis in very preterm infants. PloS one. 2017;12:0186936.
[11] Clark RH, Chace DH, Spitzer AR, Pediatrix Amino Acid Study G. Effects of two different doses of amino acid supplementation on growth and blood amino acid levels in premature neonates admitted to the neonatal intensive care unit: A Randomised, controlled trial. Pediatr. 2007;120:1286-96.
[12] Blanco CL, Gong AK, Green BK, Falck A, Schoolfield J, Liechty EA. Early changes in plasma amino acid concentrations during aggressive nutritional therapy in extremely low birth weight infants. J Pediatr. 2011;158:543-48.
[13] Balasubramanian H, Nanavati RN, Kabra NS. Effect of two different doses of parenteral amino acid supplementation on postnatal growth of very low birth weight neonates–A Randomised controlled trial. Indian Pediatr.2013;50:1131-36.
[14] Valentine CJ, Fernandez S, Rogers LK, Gulati P, Hayes J, Lore P, et al. Early amino-acid administration improves preterm infant weight. J Perinatol. 200929:428-32.
[15] Vlaardingerbroek H, Vermeulen MJ, Rook D, van den Akker CH, Dorst K, Wattimena JL, 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. 2013163:638-44. e5.
[16] NNF Evidence based clinical practice gudelines Oct 2010 by National Neonatology Forum.

[17] Gnigler M, Schlenz B, Kiechl-Kohlendorfer U, Rüdiger M, Navarro-Psihas S. Improved weight gain in very-low-birth-weight infants after the introduction of a self-created computer calculation program for individualized parenteral nutrition. Pediatr Neonatol. 2014;55:41-47.

[18] Denne SC, Karn CA, Ahlrichs JA, Dorotheo AR, Wang J, Liechty EA. Proteolysis and phenylalanine hydroxylation in response to parenteral nutrition in extremely premature and normal newborns. J Clin Invest. 1996;97:746.

[19] M Ho, Y Yen, H Chen, S Chien, M Hsieh and Y Yang. Effect of aggressive early high-dose intravenous amino acid infusion and early trophic enteral nutrition on very low birth weight infants. Food and Nutrition Sciences. 2012;3(11):1604-08. doi: 10.4236/fns.2012.311209 http://dx.doi.org/10.4236/fns.2012.311209

[20] Bonsante F, Iacobelli S, Latorre G, Rigo J, De Felice C, Robillard PY, et al. Initial amino acid intake influences phosphorus and calcium homeostasis in preterm infants-it is time to change the composition of the early parenteral nutrition. PLoS One. 2013;8:72880.

AUTHOR(S):

1. Rakesh Gami
2. Manisha Bhandankar

PARTICULARS OF CONTRIBUTORS:

1. Postgraduate Student, Department of Paediatrics, KAHER's Jawaharlal Nehru Medical College, Belagavi, Karnataka, India.
2. Professor, Department of Paediatrics, KAHER's Jawaharlal Nehru Medical College, Belagavi, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Manisha Bhandankar,
Department of Paediatrics, KAHER's Jawaharlal Nehru Medical College, Belgaum-590010, Belagavi, Karnataka, India.
E-mail: manishabhandankar@yahoo.com

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