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Original Research Article

Effects of total parenteral nutrition on postnatal growth in very low birth weight and extremely low birth weight newborns

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ABSTRACT

Background: Prematurity is the most important cause of mortality in Under-5 children responsible for one million deaths/ year. Premature babies are not able to store enough nutrients for their optimal survival; it is essential to provide them total parenteral nutrition. Intravenous lipid infusion in neonates is linked with high risk of sepsis and thrombocytopenia. PN with amino acids and glucose can be imparted to achieve nutritional goal. This trial was intended to assess the effects of various components of amino acid PN on postnatal growth in VLBW and ELBW newborns.

Methods: A prospective observational study was conducted from January 2018 - May 2019 in NICU of TMMC and RC which included preterm newborns with birth weight of less than 1500gms who received aminoven infusion. Anthropometric measurements, incidence of hypo/hypercalcaemia, hypo/hyperglycaemia, direct hyperbilirubinemia, incidence of sepsis were evaluated.

Results: Out of 22 patients, 12 neonates received high dose aminoven therapy whereas 10 neonates received low dose aminoven therapy. It was seen that rapid rate of increment of amino acids had adequate weight on discharge, 72.72% have adequate growth among the rapid group compared to 36.36% among slower group. No significant changes in calcium metabolism or glucose metabolism were seen in both the groups.

Conclusions: In resource limited settings, parenteral nutrition with intravenous amino acids have a better effect on the weight of preterm newborns at discharge when high doses of amino acids infusion started early with rapid increment in the dose.

Keywords: Aminoven, Extremely low birth weight, Postnatal growth, Total parenteral nutrition, Very low birth weight

INTRODUCTION

Approximately 15million babies are born premature worldwide every year i.e. more than one out of ten births and these numbers are rising. Prematurity is the one of the most important cause of mortality in Under-5 children responsible for roughly one million deaths every year (WHO). Among all countries, India constitutes the maximum number of preterm births, almost 24% of the total number. More than one million out of 15 million babies die shortly after birth and innumerable others suffer from various lifelong physical, neurological and educational disability causing a great burden to families and society. Babies which are born premature (before 37wks) have completely distinct nutritional needs than babies born at full term (37wks-42wks). Premature babies are frequently admitted in the neonatal intensive care unit (NICU), where they are cautiously monitored and ensured the precise balance of fluids, minerals such as sodium and potassium (electrolytes), and nutrition till full maturation of their body.

Premature babies are not able to store enough nutrients for their optimal survival; hence it is essential to provide them supplements. Postnatal nutritional intake should ideally be directly proportional to in-utero fetal growth rate.[1] However this goal is challenging and postnatal growth failure is a common problem.[2,3] The amino acid (AA) uptake by the premature newborn is far in excess of that which is provided to meet its requirement which is utilized for energy production. When fetal life is interrupted by premature birth, significant protein deficits can occur which are difficult to recover. A protein intake of approximately 3 gm/kg/day (3.85 gm/kg/day in extremely low birth weight (ELBW) newborns) and an energy intake of 90kcal/kg/day sustain intrauterine rates of growth and nitrogen accretion in newborns.[4]

ELBW infants receiving only carbohydrate as a substrate can lose 1% to 2% of their endogenous protein stores or 0.6 to 1.1 grams of protein per kg per day. Protein losses in the neonate receiving intravenous glucose increase with decreasing gestational age.[5] Delaying the AA intake in a preterm infant could potentially result in a catabolic state of nutrition, primarily leading to early postnatal growth failure and a widening gap in lean body mass between neonates and fetuses of the same gestational age.[4]

The nutritional need of a premature infant is characteristically dependent upon parenteral nutrition (PN) provided during the early postnatal life, especially for very low birth weight (VLBW) infants (birth weight of less than 1500g). In these VLBW infants, full enteral feedings are essentially postponed because of the seriousness of medical problems associated with prematurity, such as immature lung function (which frequently requires endotracheal intubation and mechanical ventilation), hypothermia, infections, and hypotension. In addition, early enteral feeds are also delayed because of concern of aggressive feeding leading to complications, such as feeding intolerance or necrotizing enterocolitis. Partial parenteral nutrition (PPN) is a supplemental form of nourishment delivered intravenously in patients who are sick or injured and in whom a feeding tube cannot be used. This nutritional supplement is only used for a short period of time until the full recovery of the baby or until establishment of normal feeds. Glucose, amino acids, salts, lipids, and vitamins are combined in varying amounts in the PPN to meet the needs of the patient.

Postnatal growth of very low birth weight (VLBW) neonates has constantly stayed a challenge in NICU. One of the major problems encountered in VLBW newborns is to determine the mode of nutrition to be offered eg. TPN, PPN or Enteral feed and the period of life it should be commenced. Premature infants frequently receive nutritional support via parenteral nutrition due to many medical and surgical causes. The AAP Committee on Nutrition reported that the rate of postnatal growth of very preterm babies as compared to that of a normal fetus of the same postmenstrual age is rarely met even after providing adequate nutrition.[5] After birth, most of the infants lose 10% to 20% of their birth weight. Half of this loss is due to extracellular water loss, but the remainder represents either loss or failure to accrete lean mass and/or fat at a reasonable rate.[6] Time to regain birth weight could be longer and catch-up requirements are higher in these babies. Undernutrition through early periods has permanent effects on various aspects of development, cognition and behavior as well as somatic growth.

Early aggressive nutritional management as an answer to postnatal growth failure has been studied. The evidence corroborate with the recommendations to administer early parenteral nutrition and enteral nutrition.[7] There is evidence from various randomized controlled trials that early amino acid supplementation (starting within few hours of birth) as compared to amino acid supplementation after 3-5 days of life, in very preterm babies, results in better post-natal growth.[8,9]

In resource limited settings such as in developing countries, providing total parenteral nutrition (TPN) is often arduous with increased complication rates. Intravenous lipid infusion in neonates is often linked with high risk of sepsis and thrombocytopenia. In such case scenarios, PN with amino acids and glucose can be imparted to achieve nutritional goal. Authors undertook this trial in order to assess the effects of various components of amino acid PN on postnatal growth in very low birth weight (VLBW) and extremely low birth weight (ELBW) newborns.

METHODS

A prospective observational study was conducted from January 2018 to May 2019 in NICU of TMMC&RC after obtaining the consent of the parents.

Inclusion criteria

All preterm newborns with birth weight of less than 1500gms admitted in NICU who received aminoven infusion were included in the study.

Exclusion criteria

Infants with birth asphyxia, congenital malformations and who underwent any surgical procedure were excluded from the study.

All babies received dextrose infusion from day 1 with volume of fluid customized as per day of life (ml/kg/day). Oxygen therapy, respiratory support and IV antibiotics were given if required. Amino acid infusion was started in different doses and at different day of lives in preterm babies according to the preferences of unit incharge and it was discontinued when the babies were accepting 75% of total fluid requirement as enteral feeds.

All babies were classified in groups as per starting dose of amino acids (high=2gm/kg/day and low-1gm/kg/day), amino acids started at day of life (early- within 24hrs and late- after 24hrs) and number of days required to achieve maximum(3gm/kg) dose (rapid- within 5 days and slow-more than 5 days).

Anthropometric measurements (weight, length, ofc) were recorded daily by the NICU staff till the time of discharge with weight monitoring on an electric weighing scale in the morning daily. Adequate postnatal growth at discharge was defined by adequate weight gain plotted on Ehrenkranz postnatal growth curve i.e. discharge weight lying between±1SD on growth chart. Growth failure was described when discharge weight of babies was below -1SD on postnatal growth chart.

Other parameters like incidence of hypo/hypercalcaemia, hypo/hyperglycaemia, direct hyperbilirubinemia and incidence of sepsis were also evaluated. Blood glucose monitoring was done every 6hourly for the first 72hrs of life in all babies and thereafter if required. Sepsis screen and blood C/S were sent if clinically indicated or in presence of risk factors. Serum calcium levels checked in all babies on 3rd day of life or when clinically indicated. Breast milk was preferably used in all babies.

RESULTS

A total of 22 patients were enrolled in the study. After determining proportions of patients, association between anthropometric changes with duration and dose of amino acids were calculated. Fischer z test is used for statistical analysis to test the level of significance between proportions and Odds ratio is used to show the ratio between proportions.

Out of 22 newborns included in the study, distribution of the patients was done according to their birth weight and sex. 18 newborns lie in VLBW category (1000-1499gms) whereas only 4 newborns weigh <1000gms i.e. ELBW category. Out of the total number of patients, 14 were male and 8 were females (Table 1).

Table 1: Distribution of weight groups according to birth weight and sex.

Birth weight (in gms)	Male	Female	Total
<1000	2	2	4
1000-1499	12	6	18
Total	14	8	22

The effect of starting high dose amino acids (2gm/kg/day) v/s low dose amino acids (1gm/kg/day) on the growth of the patients was seen. Out of 12 patients in high amino acids category, 9(75%) of them showed adequate growth whereas only 3(25%) patients showed inadequate growth. 10 patients were started with low amino acids, 3(30%) among them showed adequate growth while 7(70%) showed inadequate growth. Z value =2.35, p-value <0.05 which was found to be significant. The odds ratio is 7.0 showing adequate growth with high dose of amino acids (Table 2).

Table 2: Effect of dose of amino acid on adequate growth.

Dosage	Adequate growth	Inadequate growth	Total
High Amino acid (n=12)	9(75%)	3(25%)	12
Low Amino acid (n=10)	3(30%)	7(70%)	10
Total	12	10	22

The effect of rate of increment of amino acids on adequate growth was also studied. Out of 11 patients in rapid increment category (max within 5 days), 8(73%) showed adequate growth and 3(27%) had inadequate growth on discharge. Out of 11 patients in slow increment category (max after 5 days), only 4(36%) showed adequate growth and 7(64%) had inadequate growth on discharge. Z value=1.83, P-value <0.05 which was found to be significant. The odds ratio is 4.67 showing adequate growth with rapid increment in doses of amino acids (Table 3).

Table 3: Effect of rate of increment of amino acid on adequate growth.

	Adequate growth	Inadequate growth	Total
Rapid(n=11)	8(72.72%)	3(27.27%)	11
Slow(n=11)	4(36.36%)	7(63.63%)	11
Total	12	10	22

The effect of the day of starting of the amino acids was also seen on adequate growth. Out of 12 newborns included in early category (within 24hrs of birth), 7(58%) showed adequate growth while 5(42%) showed inadequate growth. Out of 10 newborns included in late category (after 24hrs of birth), 5(50%) showed adequate growth while 5(50%) showed inadequate growth. Z value=0.39, p-value >0.05 which was not significant. The odds ratio is 1.4 (Table 4).

Table 4: Effect of day of starting of amino acid on adequate growth.

	Adequate	Inadequate	Total
Early (n=12)	7(58.33%)	5(41.66%)	12
Late (n=10)	5(50%)	5(50%)	10
Total	12	10	22

The effect of doses of amino acids on glucose metabolism was also studied. Out of 12 patients included in high amino acid group, 3(25%) had normal glucose metabolism whereas 9(75%) had abnormal glucose metabolism. Out of 10 patients included in low amino acid group, 4(40%) had normal glucose metabolism whereas 6(60%) had abnormal glucose metabolism, z value =0.75, p-value >0.05 which was not significant. Odds ratio is 0.5 (Table 5).

Table 5: Effect of dosage of amino acid on glucose metabolism abnormalities.

	Normal glucose value	Abnormal glucose value	Total
High amino acid(n=12)	3(25%)	9(75%)	12
Low amino acid(n=10)	4(40%)	6(60%)	10
Total	7	15	22

The effect of dose of amino acids was also studied on calcium metabolism. Out of 12 patients in high dose category, 9(75%) had normal calcium levels in the body while only 3(25%) had abnormal calcium levels. Out of 10 patients in low dose category, 6(60%) had normal calcium levels in the body while 4(40%) had abnormal calcium levels, z value =0.75, p-value >0.05 which was not significant. The odds ratio is 2.0 (Table 6).

Table 6: Effect of dosage of amino acid on altered calcium metabolism.

	Normal calcium value	Abnormal calcium value	Total
High Amino acid(n=12)	9(75%)	3(25%)	12
Low amino acid(n=10)	6(60%)	4(40%)	10
Total	15	7	22

Table 7: Effect of dosage of amino acid on sepsis.

	Sepsis	No sepsis	Total
High amino acid (n=12)	10(83.33%)	2(16.66%)	12
Low amino acid (n=12)	8(80%)	2(20%)	10
Total	18	4	22

Incidence of sepsis due to the effect of dosage of amino acids was also studied. Out of 12 newborns in high amino acid group, 10(83%) had evidence of septicemia while 2(17%) showed no evidence of sepsis. Out of 10 newborns in low amino acid group, 8(80%) had evidence of septicemia while 2(20%) showed no evidence of sepsis. Z value =0.20, p-value >0.05 which was not significant. The odds ratio is 1.25 (Table 7).

DISCUSSION

Out of 22 patients enrolled, 4 neonates were ELBW while 18 neonates were VLBW. Out of them, 12 neonates received high dose aminoven therapy whereas 10 neonates received low dose aminoven therapy. Effect of dose, rate of increment, day of starting aminoven was analyzed on growth, glucose metabolism, calcium metabolism and incidence of sepsis. It was found that early start and high dose of amino acid (2g/kg/day) resulted in better growth of the newborn when plotted on Ehrenkranz postnatal growth curve. It was also seen that rapid rate of increment of amino acids (within 5 days of life) had significant outcome (adequate weight on discharge), p<0.05, CI-0.7509-0.237.

In this study, babies who received rapid increment of amino acids (3g/kg/day within 5 days of life) had better growth at discharge. 72.72% have adequate growth among the rapid group compared to 36.36% among slower group (p<0.05). It also showed that 58.33% babies in early amino acid group (within 24 hrs) had adequate growth as compared to the late amino acid group (after 24hrs of life) though p value was not significant. No significant changes in calcium metabolism or glucose metabolism were seen in both the groups.

Tang et al, studied high dose amino acid (2.4gm/kg/day) administration in preterm babies starting within 24hrs of birth and increasing by 1.2g/kg/day to a maximum of 3.6g/kg/day compared with newborns who received medium dose (1g/kg/day), starting 24hrs after birth, increasing by 0.5g/kg/day to 3g/kg/day as final dose. Intensive and early administration of amino acids was found to improve growth and tolerance to enteral feeding.[10]

Clark et al, studied the effect of two different dosages of aminoacid supplementation (starting dose of 1g/kg/day in one group and 1.5g/kg/day in other group to maximum of 2.5g/kg/day) on growth of premature newborns and their blood amino acid levels. They showed that higher dose of amino acid supplementation did not improve neonatal growth whereas it was associated with increase in blood amino acids and urea nitrogen level.[11]

Valentine et al, showed a significantly greater weight gain in preterm infants who were given amino acids early (within 24hrs of birth) as compared to the group supplemented late with an advantage of shorter duration of amino acid supplementation suggesting that amino acid nutrition is critical within first 24 hrs.[9]

Balasubramanian et al, showed better anthropometric measurements (weight, length, ofc) in the group who were given lower doses of amino acids supplements compared to early aggressive partial parenteral supplementation in very low birth weight infants due to inadequate non-protein calorie intake.[12]

Poindexter et al, reported significant differences in anthropometric growth outcome (wt, lt, hc) at 36wks PMA in infants who received early AA compared to the late AA group but there were no differences (anthropometric, neurodevelopmental) seen at 18 months CA in both groups.[13]

Kotsopoulos et al, showed that early amino acid administration is associated with reduced incidence of sepsis and is effective in reducing the time to regain the birth weight in ELBW infants. It also proved that it was not associated with any clinically significant adverse effects or metabolic acidosis.[14]

Heimler et al, studied the effect of early versus late administration of the amino acid in preterms and the outcomes suggested that there was no difference in the head circumference, serum glucose and blood ammonia levels but the group that received AAs early had positive nitrogen balance and elevated serum BUN.[15]

Some other studies 16-19 have shown that starting higher doses of amino acids from day 1 results in better plasma amino acid profile and are well accepted, but its role in improving post-natal growth rate and long term neurodevelopmental outcome is still inconclusive.

Limitations of the study is less sample size of the study as fewer number of neonates stayed in the NICU of the institute for longer periods till fulfillment of discharge criteria and short study period.

CONCLUSION

In resource limited settings, parenteral nutrition with intravenous amino acids have a better effect on the weight of preterm newborns at discharge. Starting high doses of amino acids infusion (2g/kg/day) has a beneficial effect with rapid increment in the dose (reaching to 3mg/kg/day within 5 days of life) is associated with better weight gain at discharge of the preterm newborn.

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