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A Study of Effect on Weight Gain by High Dose Amino Acid Infusion Vs Low Dose Amino Acid Infusion in Preterm Very Low Birth Weight Infants Admitted in Nicu in A Tertiary Care Hospital

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ABSTRACT

Background: Premature infants have higher mortality rates and are more prone to a variety of morbidities compared to term babies. The immaturity of the organs or functions is a contributing factor for many of the issues that preterm infants face. Hyaline membrane disease, patent ductus arteriosus, intraventricular haemorrhage, and metabolic issues including hypoglycaemia and NEC (necrotising enterocolitis) are some of the major complications/morbidities associated with premature birth. In addition, feed intolerance is a common gastrointestinal issue in preterm new-borns.

Aims and Objectives: To study, the effect of Early administration of High Dose amino acid infusion Vs Low Dose Amino Acid infusion on Weight Gain in Preterm very low birth weight infants admitted in NICU in Krishna Hospital, Karad and compare the effects.

Material and Methods: Study design: This was a hospital based interventional study done on 60 preterm vlbw infants admitted in to Neonatal ICU of tertiary care hospital of Karad from December 2020 to December 2022.

Statistical Analysis: The statistical analysis was done with SPSS software version 22. Mean, standard deviation was calculated for continuous variables to know their central tendency. Chi square test was used to test the association between categorical variables and t test for continuous variables. A $p<0.05$ was taken as significant.

Results: majority of the newborns were born at a gestational age of 32 nd -34th weeks in both the study groups (65.4%) (moderate preterms) and 28th -30th weeks of gestational age in both the study groups (34.6%) were very preterms, weight gain during hospital stay was compared among the two study groups, we observed statistically significant weight gain in high dose aminoacid group when compared to low dose amino acid group

Conclusion: This study suggests that high doses of Aminoacid infusions in the early Parenteral nutrition facilitate weight gain in preterm vlbw infants and also early recovery of birth weight with early achievement of full enteral feeding when compared to low doses of aminoacid infusion.

Keywords: *Early amino acid infusion EAA , Hospital based interventional study*

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INTRODUCTION

Premature infants have higher mortality rates and are more prone to a variety of morbidities compared to term babies. The immaturity of the organs or functions is a contributing factor for many of the issues that preterm infants face.

Hyaline membrane disease, patent ductus arteriosus, intraventricular haemorrhage, and metabolic issues including hypoglycaemia and NEC (necrotising enterocolitis) are some of the major complications/morbidities associated with premature birth. In addition, feed intolerance is a common gastrointestinal issue in preterm new-borns.

The infant needs to be kept on intravenous fluids for extended periods of time, and feedings have to be gradually introduced. Additionally, due to their frequent negative nitrogen balance and other morbidities, the calories provided may not be utilised for growth in these new-borns. Because of the functional immaturity of the gut, premature new-borns frequently are unable to absorb the vital components of milk like their term counterparts.

As per American Academy of Paediatrics guidelines 1985, it is desirable that all preterm infants must now meet a standard of postnatal nutrition that equals healthy prenatal development rates1 . There is increased number of very preterm infants surviving thanks to the improvements in perinatal care. These new-borns' specific nutritional and metabolic needs for growth are determined by their low energy reserves, high protein flow rate, and high metabolic rate as a result of a disproportionately greater mass of metabolically active organs. However, due to concerns about feed intolerance, it is routine practise in many newborn intensive care units to restrict nutritional administration, particularly amino acid administration, to ELBW or ill neonates in the early neonatal period. Several studies suggest that this delay in nutrition results in postnatal malnutrition that produces measurable growth failure at hospital discharge[2-4].

There are reasons to believe that concentrating on protein supply may be particularly important, even though measures to promote growth entail delivery of larger amounts of both energy and protein beginning soon after birth.[5]. Data from studies in animal foetus models suggest that amino acid metabolic rates 2 may be a much more sensitive indicator than growth rate of adequate nutrition before term [6].

Additionally, recent data suggest that long-term developmental outcome in the preterm may be correlated with early protein intake[7].

We conducted this prospective, randomised study in very preterm neonates of early parenteral administration of "low" versus "high" amino acid intake in order to assess the efficacy and safety of early amino acid intake rates that more closely resemble foetal birth rates. In this study 1.0 g/kg/day (Low amino acid group) or 3.0 g/kg/day (High amino acid group) amino acids groups were compared to assess the effects on pattern of growth (weight) in Preterms weighing less than 1.5kg.

MATERIALS AND METHODS

Objectives

The objectives of this study are to to study the effect of early administration of High dose amino acid and Low dose Aminoacid on Weight gain in Preterm very low birth weight infants and to compare the effect of High dose amino acid Vs Low dose Aminoacid infusion on pattern of growth and duration of achievement of full enteral feeding in Preterm vlbw infants.

Inclusion Criteria

All inborn preterm newborns of Birth weight ≤1500 gms and Appropriate for Gestational Age and small for Gestational age admitted in NICU in a tertiary care hospital who were haemodynamically and clinically stable, except for Respiratory distress were included in the present study.

Exclusion Criteria

Term Babies • Congenital malformations. • Congenital Heart Disease babies • Hemolytic disease of new-born • Preterm babies with derranged Liver Function • Preterm babies with deranged Renal Function • Preterm babies who were diagnosed with sepsis later on after including in the study • Preterm babies went into Necrotising enterocolitis later on after including in study • Metabolic disorders • Newborns receiving Fresh Frozen Plasma and whole blood transfusions • Newborns with congenital anomalies or inborn errors of metabolism (IEM),

needing surgery, discharged as against medical advise, and death during NICU stay

Study Design

The study was a hospital based interventional study done on 60 preterm vlbw infants admitted in to Neonatal ICU of tertiary care hospital of Karad from December 2020 to December 2022 after taking clearance from institutional ethical committee of KRISHNA HOSPITAL, KARAD.

Statistical Analysis

The data was collected with the help of standard, semi-structured, pre-validated case record proforma.

The data was entered with the help of MS excel software and was represented in the form of tables and charts for frequency analysis. The statistical analysis was done with SPSS software version 22. Mean, standard deviation was calculated for continuous variables to know their central tendency. Chi square test was used to test the association between categorical variables and t test for continuous variables.

P-value less than 0.05 was considered to be statistically significant.

RESULTS

In this study, it was observed that majority of the newborns were born at a gestational age of 32 nd -34th weeks in both the study groups (65.4%) (moderate preterms) and 28th -30th weeks of gestational age in both the study groups (34.6%) were very preterms. • The mean birth weight of Low aminoacid group was 1150.76±124.31g , whereas in High amino acid group it was 1143.38±166.95g • In the present study, weight gain during hospital stay was compared among the two study groups, we observed statistically significant weight gain in high dose aminoacid group when compared to low dose amino acid group. • In the present study, the duration of hospital stay in High dose amino acid group (17.92±9.87 days) was less when compared to the low dose aminoacid group (20.57±9.41 days), though not statistically significant difference was observed ($p > 0.05$) • The mean initiation of enteral feeding was earlier in High dose aminoacid group (4.04±2.49) days than those in low dose aminoacid group (6.53±3.73) days with a statistically significant difference (p 0.006). • The mean age for recovery of birth weight was earlier in High dose aminoacid group (5.48±1.39) compared to low dose aminoacid group(8.46±1.88) with a statistically significant difference (p 0.001) • No significant differences were observed in the comparision of length and head circumference parameters on D1, D7, D14 and day of discharge during hospitalization between both groups. • In our study, we assessed for Total leucocytic count,haemoglobin and platelet count as the components of sepsis screen on D1 , D7, D14 in 59 each group and compared among both the groups , We observed that there is no significant difference between two groups. • In our study, we assessed for blood cultures in all study neonates and 7 babies out of 52 had positive blood cultures. Out of 7 culture positive babies, 5 babies had klebsiella as isolated organism and 2 babies had acinetobacter as isolated organism however when compared between two groups we observed that there is no significant difference between two groups. • In the present study we assessed for blood urea,serum creatinine and blood urea nitrogen on D1, D7, D14 in each group and both the groups were compared,we We observed that there is no significant difference between two groups. • In our study, we assessed for blood cultures in all study neonates and 7 babies out of 52 had positive blood cultures. Out of 7 culture positive babies, 5 babies had klebsiella as isolated organism and 2 babies had acinetobacter as isolated organism however when compared between two groups we observed that there is no significant difference between two groups. • In the present study we assessed for blood urea,serum creatinine and blood urea nitrogen on D1, D7, D14 in each group and both the groups were compared, we observed no significant difference between 2 groups. • Furthermore, no significant differences were observed in other laboratory findings like serum electrolytes on the 1st, 7th , and 14th day during hospitalization between both groups.

TABLE 1: Gestational age (weeks)

Gestational age (wks)	Low dose amino acid group		High dose amino acid group		Total	
	N	%	N	%	N	%
28^{th} – 30^{th} weeks	9	34.6%	9	34.6%	18	34.6%
32^{nd} – 34^{th} weeks	17	65.4%	17	65.4%	34	65.4%
Total	26	100%	26	100%	52	100%
Mean GA	31.15 ± 1.82		31.19 ± 1.91		31.17 ± 1.85	
P	Unpaired t test, t-statistic= 0.079 p=0.937					

TABLE 2: Average Birth weight comparison

	Minimum (grams)	Maximum (grams)	Mean ± SD
Low dose aminoacid group	900	1320	1150.76±124.31
High dose aminoacid group	725	1350	1143.38±166.95

TABLE 3: Duration of Hospital stay (days)

Duration of Hospital stay (days)	Minimum (days)	Maximum (days)	Mean ± SD	P
Low Dose Aminoacid Group	7	35	20.57 ± 9.41	0.326
High Dose Aminoacid Group	4	40	17.92 ± 9.87	

TABLE 4: Initiation of enteral feed (age in days)

	Minimum (age in days)	Maximum (age in days)	Mean ± SD	P
Low Dose Aminoacid Group	2	18	6.53 ± 3.73	0.006
High Dose Aminoacid Group	2	10	4.04 ± 2.49	

TABLE 5: Weight Monitoring during hospital stay

Weight (kg)	Low Dose Aminoacid Group		High Dose Aminoacid Group		P value
	Mean	SD	Mean	SD	
D1(day 1)	1.15	0.12	1.14	0.17	0.84
D7(day 7)	1.14	0.13	1.28	0.20	0.00*
D14(day 14)	1.31	0.13	1.42	0.19	0.05
Discharge	1.51	0.03	1.65	0.11	0.00*

TABLE 6: Comparison of average duration of Recovery of birth weight (age in days)

Recovery Of Birth Weight (Days)	Low Dose Aminoacid Group (Age In Days)		High Dose Aminoacid Group (Age In Days)		P Value
	Mean	SD	Mean	SD	
Recovery of birth weight	8.46	1.88	5.48	1.39	**0.001***

DISCUSSION

In the first few weeks of life, preterm newborns require between 80 to 120 Kcal per kilogram of body weight, as endorsed by several Guidelines on Paediatric Parenteral Nutrition including the ones released by European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR) (2005).

In 2006 Ehrenkranz RA et al reported that growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants therefore preterm infants must receive early, enough feeding to improve their neurodevelopmental outcome.

We In the present study, neonates were consecutively randomized into two groups Group A and Group B and were administered low dose (1g/kg/day) and high dose (3g/kg/day) of parenteral Amino acid preparation respectively. Group A received 1 g/kg/day of parenteral Aminoacids on day one and dose was increased by 1 gm/kg/day every day till maximum of 3.5 gm/kg/day. Group B received 3 gm/kg/day of parenteral Amino acids on day one and dose was continued till 75% of full enteral feed was achieved. On day one, Partial Parenteral Nutrition was administered to the neonates in both groups, which comprised of dextrose (glucose infusion rate (GIR) 6-8 mg/kg/min), Aminoacids, calcium. Intra Lipid supplementations were not given in the study,**Wilson et al (1997)**[8] in their study, started the amino acid infusion at a dose of 0.5 g/kg/ day at 12 hours of life in aggressive group Vs 1 g/kg/day on day 3 of life in slow group with daily increment of 0.5 g/kg/day reaching a maximum dose till 3.5g/kg/day in aggressive vs 2.5g/kg/day in slow group.We found that, 24(40%) neonates were very low birth weight (VLBW), 15(25%) neonates were low birth weight (LBW) and 21(35%) neonates were of normal birth weight. There were no extreme low birth weight (ELBW) or overweight babies in our study.

Effect of Total Parental Nutrition on Anthropometric measurements

The average birth weight, of Low aminoacid group was 1150.76±124.31g , whereas in High amino acid group it was 1143.38±166.95g which suggests that at baseline, there existed no significant difference in the birth weights of the two intervention groups.(Table 3) At discharge the average weight in Low amino acid group was 1.51 ± 0.03 Kg whereas the average weight at discharge in High Amino acid group was 1.65 ± 53 0.11 Kg. The difference in weight at discharge was found to be statistically significant (p<0.001)

The average weights on day 7 and day 14 in High Amino acid group was also significantly higher than low dose amino acid group. **Valentine et al 2009**[9] compared early amino acid administration to late amino acid in preterm infants and came to the conclusion that weight gain is better in the early higher amino acid group with a difference in adjusted mean weight gain between the two groups being 51.28g (95%CI; 3.76 - 98.81). Analysis at 36 weeks Corrected gestational age indicated fewer infants below 10th centile in early amino acid group (23.7%) vs late amino acid group (41.7%) (p

Regaining Birth Weight

The recovery of birth weight in the two groups was compared, and found birth weight recovery was earlier in High dose aminoacid group 5.48±1.39 days compared to Low dose aminoacid group 8.46±1.88 days. This was statistically significant difference (p= 0.001) 54 In the study by **Tan et al 2005** [10] there was a statistically significant difference in the mean days to regain birth weight: 10.3 days in the intervention group vs 13.9 days in the control group (p<0.001).

Initiation of Enteral Nutrition

We compared the number of days required for initiation of enteral feed in both groups , the mean start of enteral feed in Low dose amino acid group was 6.53±3.73 day of life, whereas in high dose amino acid group it was 4.04±2.49 day of life. The earliest days required for initiation of enteral feed in both the groups was 2 nd day of life and the most late day required for initiation of enteral feed in Low aminoacid group was 18th day of life and in High dose aminoacid group, it was 10th day of life. The Initiation of Enteral feed in high amino acid group was Earlier in comparision to Low aminoacid group, **Tan et al 2005**[10] , in their study, studied the duration to

reach full enteral feeds and observed that it took around 19th day of life to reach full enteral feeds in the intervention group compared to 15th day of life in the control group. **Wilson et al(1997)**[8] noted that the number of days to reach full feeds showed a median interquartile range of 13th - 30th day of life in aggressive group (Amino acid solution was started at 0.5 g/kg/ day at 12 hours with increments of 0.5 g/kg/day to a maximum of 2.5 g/kg/day) vs 16th -30 th day of life in slow (Amino acid solution (Aminoplasmal Paed, B Braun Medical Ltd) was started at 1 g/kg/day on day 3 and increased by 0.5 g/kg/day to a maximum of 2.5 g/kg/day) group.

Comparison of Complications

In the present study we assessed for complications in both the groups, we observed one neonate (3.6%) had Necrotizing entero colitis (NEC) stage IIA (according to Modified Bell s staging) diagnosed clinically and radiologically (erect x ray abdomen s/o pneumatosis intestinalis) in high dose amino acid group at the age of 10th day, who later developed septicemia and died at the age of 12th day and so was excluded from the study. **Freeman et al** [11]in their study of 115 preterm vlbw neonates, noted that lipid infusion was associated with coagulase negative staphylococcus infection; odds ratio was estimated to be 5.8 (95%CI 4.1-8.3). **Ibrahim et al 2004** in their prospective RCT study of 32 ventilator-dependent preterm infants ,compared common morbidities of prematurity like BPD, IVH, PDA, ROP (BPD 8 vs 9) in aggressive(The Early Total Parenteral Nutrition (ETPN) group received 3.5 g/kilo-day amino acids (AA), and 3 g/kilo-day of 20% Intralipid (IL), starting within 1 hour after birth) vs standard group(The Late Total Parenteral Nutrition group (LTPN), started on a solution containing glucose during the first 48 hours of life, followed by 2 g/kilo-day of AA and 0.5 g/kilo-day of IL) respectively p= 0.71; IVH 5 vs 4, p =0.45; PDA 7vs7, p =1.00; ROP 3 vs 2, p= 0.74). There was no statistically significant difference in incidence of IVH, PDA, ROP between the two groups.

Duration of Hospital Stay

In the present study Duration of hospital stay was compared among the two study groups, which showed duration of hospital stay in High dose aminoacid group (17.92±9.87) days was less when compared to the low dose aminoacid group (20.57±9.41) days. The discharge criteria of our study was till 34 weeks of corrected gestational age and weight at discharge > 1.5 kg. **tan fransica dian et al** in their 9 RCT studies with a sample size of 960 neonates observed that administration of early high-dose amino acids reduced the time to regain birth weight and the length of hospitalization in preterm infants.

Mortality

In the present study One neonate in the high amino acid group had septicemia and died on 12th day of life so was excluded from the study. Mortality was compared between the two groups in various other studies. Ibrahim et al 2004 72 could not find any statistically significant difference in mortality between the groups (Early Total Parenteral Nutrition (ETPN) group received 3.5 g/kilo-day amino acids (AA), and 3 g/kilo-day of 20% Intralipid (IL), starting within 1 hour after birth and Late Total Parenteral Nutrition group (LTPN), started on a solution containing glucose during the first 48 hours of life, followed by 2 g/kiloday of AA and 0.5 g/kilo-day of IL). though sample size was (32 sick neonates) low. Wilson et al (1997) 68 compared mortality among 2 groups conservative group (AA- 2.5g/kg/day + 2g/kg/day lipid) vs aggressive group (AA- 3.5g/kg/day + 3.5g/kg/day lipid) and noticed that odds ratio was 0.9 (95%CI 0.4-2.1) which was not statistically significant.

Limitations

1) The children were followed up till the discharge however, post discharge follow up was not maintained due to time constraints thus the lack of long term outcomes is one of the limitation of the study.
2) ABG or serum Bicarbonate were not studied.
3) Volume of Trophic feeds given were not compared.
4) Intravenous lipids were not used in the present study.

CONCLUSION

1. This study suggests that high doses of Aminoacid infusions in the early Parenteral

nutrition facilitate weight gain in preterm vlbw infants and also early recovery of birth weight when compared to low doses of aminoacid infusion.

2. This study also suggests that high doses of Aminoacid infusions in the early Parenteral nutrition facilitate early achievement of full enteral feeding in preterm very low birth weight infants when compared to low doses of aminoacid infusion.

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