

A comparative study of low dose (1gm/Kg/Day) vs high dose (3gm/kg/day) protein parenteral nutrition therapy on nutrition accretion and outcomes in very low birth weight preterm neonates-a randomized controlled trial

M. Sujeeth Kumar¹, A. Akshay Reddy^{2*}, M Padmanabh Reddy³, Sudha Boda⁴, Uma Raju⁵

¹Senior Resident Pediatrics, ²Neonatology Fellow, ³Consultant Neonatology & Director, ^{4,5}Consultant Neonatology, ¹Apollo Medical College, Jubilee Hills, Hyderabad, Telangana, NICE Hospital for Women, Newborns & Children, Hyderabad, Telangana, India

*Corresponding Author: A. Akshay Reddy

Email: drakshayreddy2259@gmail.com

Abstract

Introduction: Parenteral Nutrition (PN) therapy plays a vital role in the management of hospitalized very low birth weight (VLBW) preterm infants who are unable to feed adequately. However, the optimal dosage of the nutrient infusate which enables accretion with best tolerance remains controversial. Hence this study was undertaken.

Aim: To compare the efficacy of low(1gm/kg/day) vs high dose (3gm/kg/day) proteins in PN therapy in pre-term VLBW neonates on nutrition accretion as evidenced by time to regain birth weight, respiratory support duration, hospitalization period and tolerance as evidenced by side-effects encountered.

Materials and Methods: This RCT study enrolled hospitalized preterm VLBW neonates who were not predicted to achieve full enteral nutrition in 5 days. Aminoacids were started on day1 in PN fluids after randomization and were increased in increments of 0.5gm/kg/day to a maximum of 4gms/kg/day. Primary outcomes were time to regain birth weight and days of oxygen dependency. Secondary outcomes were days on PN, hospitalization duration & days of Invasive/non-invasive ventilation. Complications encountered viz ROP/IVH/PDA/NNEC were recorded. Data obtained was analysed statistically.

Results: The two study groups were comparable for birth weight, gestational age, gender and delivery mode. In low dose vs high dose protein groups time to regain birth weight (13.82vs 12.91days), hospital stay (19.29vs18.69days), oxygen dependency duration (6.81vs6.82 days) were comparable ($p>0.05$) as were secondary outcomes i.e hospitalisation duration (19.29 vs18.69 days), TPN duration (7.64vs7.41days) and ventilation duration (invasive-1.71vs1.09days & non-invasive-5.04vs5.91days). Complications observed were similar except for increased incidence of IVH in low dose protein group.

Conclusions: The study suggests that low dose protein infusate is as effective as high dose proteins in PN therapy of preterm neonates.

Keywords: Preterm neonates, Parenteral nutrition, Low vs high dose proteins, Aminoacid infusate.

Introduction

Parenteral Nutrition (PN) enables to meet a neonate's nutritional requirement when its condition precludes adequate enteral feeding. In low birth weight premature infants, enteral feeding may not be effectively established in the early days of life.¹ Further, as many of these infants are critically ill, PN becomes necessary to not only meet the energy demands but also provide the increased requirements related to stress factor for disease as well as provide for growth and development.²

Intrauterine fetal growth is supported by a continuous supply of nutrients from mother to the fetus throughout pregnancy which enables optimum fetal growth. Preterm delivery leads to a disruption in delivery of nutrients to the fetus. To enable a growth rate similar to that seen in utero and prevent extra-uterine growth retardation, delivery of nutrients postnatally should be optimum. Extra-uterine growth retardation is associated with adverse outcomes and provision of appropriate nutritional requirements soon after birth is critical for normal growth and development of preterm infants.^{3,4} Further these preterm infants are often not able to tolerate volumes of oral feeds that will provide adequate daily requirements. Hence the need of parenteral nutritional therapy in the premature infants is mandatory to meet the nutritional needs and to cater for rapid growth and development which is a hallmark of their postnatal development. Parenteral nutrition involves a provision of

balanced amounts of all of nutrients required. Intravenous amino acids with or without glucose also stimulate insulin secretion which augments amino acid stimulation of protein synthesis and protein accretion. Protein must be administered with energy as it improves nitrogen retention by enhancing amino acid utilization for protein synthesis and in the absence of adequate energy sources, is broken down to produce energy for vital body needs and is thus unavailable for protein synthesis and tissue repair.⁵

While there is little doubt about the need of proteins in parenteral nutritional therapy in preterm neonates, the dose at which it needs to be provided to achieve nutritional accretion as well as a positive nitrogen balance, appears to be a grey area. While several reports of high dose proteins in TPN (3gm/kg/day starting) appear to be promising, some recent studies have suggested that low dose proteins (1gm/kg/day) PN with higher NPC/N ratio may be equally beneficial.⁶

Hence this study was undertaken to compare the nutritional accretion with low dose vs high dose proteins in parenteral nutrition therapy in VLBW preterm neonates. The outcomes studied were time taken to regain birth weight, duration of respiratory support and hospitalization period. Tolerance was assessed by side-effects encountered viz retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NNEC) and

hemodynamically significant patent ductus arteriosus (hsPDA).

Materials and Methods

This study was undertaken at a tertiary care NICU over a period of two years from September 2015 to September 2017. It was a hospital based randomized control trial in preterm very low birth weight (<1500 gms) neonates. Informed written consent was obtained from the parents for enrollment in the study. Approval of the Institutional Ethics Committee and Hospital Scientific Research Committee was obtained for the conduct of the study.

Neonates who met the inclusion criteria viz babies with a gestational age of < 37 completed weeks with birth weight of <1500grams who were not expected to establish adequate enteral feeds within 5 days. Neonates who met the inclusion criteria but had major congenital anomalies, early onset sepsis or were critically ill with organ failure were excluded from the study. Enrolled infants were assigned to low protein (1gm/kg/day) and high proteins (3gm/kg/day) groups by randomization using computer generated sequences.

Babies were weighed on an electronic weighing scale (accuracy of 5g) soon after birth and subsequently daily every morning till discharge. Ventilator and oxygen settings were regulated as per neonate's requirement. Parenteral nutrition was commenced on day 1 of admission after randomization to each group. Aminoacids in parenteral fluids were increased in increments of 0.5gm/kg/day to a maximum of 4gms/kg/day. Non protein nutrients were administered as per standard guidelines. Fluids and electrolytes were administered as per unit protocol. It was ensured that the glucose infusion rate was not < 5 mg/kg/min and was titrated with blood sugar levels. It was ensured that non-protein calorie intakes were atleast 75 Kcal/kg/day. As enteral feeds reached 50% of the total fluid intake, parenteral nutrition was tapered. Amino acid infusions were stopped once the baby was able to tolerate 75% of total intake orally. Feeds provided were predominantly expressed breast milk (EBM). Laboratory investigations carried out included complete blood picture, serum electrolytes, renal function tests, blood sugar, serum calcium, serum proteins & triglycerides monitoring as per unit protocol.

Data obtained was recorded and statistically analysed. Statistically significant sample size was calculated as per previous studies standard deviation with 10% error in each group. Mean was calculated between two groups by using Student 't' test and Chi-square test was used to calculate proportion between two groups.

Results and Analysis

Incidence

During the study period, of 1647 newborns admitted into NICU, 729 (44.27%) were preterm and 144(19.8%) babies weighed<1500grams. Of these, 84 neonates met the inclusion criteria and were enrolled in the study. Amongst them there were 6 drop outs who left against medical

advice, 7 deaths and 11 cases developed critical illness viz cardiac failure/renal failure/DIC. 60 babies completed the study. Of these 28 babies (46.7%) were provided low dose (1gm/kg/day) protein and 32 babies (53.3%) were provided high dose (3gm/kg/day) protein in parenteral nutrition.

Gender Distribution

It was observed that of the cases enrolled in the study, 31(51.7%) were males and 29(48.3%) females. Gender wise, there was even distribution of cases between high dose vs low dose protein groups as shown in Table 1.

Gestational Age Distribution

Out of 60 preterm babies, 18 (30%) neonates were between 32-36weeks gestational age, 26 (43.3%) of 30-32weeks, 13 (21.7%) of 28-30weeks and 3 (5%) neonates were extremely premature of less than 28 weeks gestational age. There was a equitable distribution as per mean gestational age in low dose protein group viz 30.89 weeks vs 31.06 weeks in high protein group as shown in Graph. 1(p=0.794).

Birth Weight-wise Distribution

In the study, 6 neonates (10%) were extremely low birth weight (<1000grams), 23 (38.3%) neonates had birth weight of 1000–1250 grams & 31 neonates (51.7%) weighed 1251 to 1500grams. The mean birth weight in the low dose protein group was 1201.2 grams vs 1239.1 grams in high dose group. There was no statistically significant difference between the two groups mean birth weight-wise (p=0.386).

Primary Outcomes

A. Time to Regain Birth Weight

In high dose protein group, the average number of days to regain birth weight was 12.91 as opposed to low dose protein group in whom it was 13.82 days shown in Table 2. Though the time taken to regain birth weight was shorter in the high protein dose group, it did not reach levels of statistical significance.

B. Days of Oxygen Dependency

In high dose protein group (3gm/kg/day), 27 babies (84.4%) required oxygen support for an average of 6.81 days vs 26 babies (92.9%) requiring it with mean dependency of 6.82 days in low dose protein group as shown in Graph 2.

There was no statistically significant difference between quantity of protein provided and oxygen dependency days (p = 0.996).

Secondary Outcomes

A. Duration of Hospital Stay

In high dose protein group average number of hospital stay was 18.69 days as opposed to low dose protein group where it was 19.29 days. Though hospitalization duration was shorter in the high protein dose groups, it did not reach levels of statistical significance (p= 0.84).

B. Duration of TPN

In the high protein group, average duration of TPN provision was 7.41 days vs 7.64 days in low proteins dosage group as shown in Table 3. There was no statistically significant difference between quantity of protein provided with regard to days of hospital stay (p = 0.843), and days of TPN requirement (p = 0.840).

C. Days of Non-Invasive Ventilation

In 3 gm proteins group, average duration of non-invasive ventilation was 5.91 days and in 1gm group it was 5.04 days as shown in Table 4. The difference in duration of non-invasive ventilation between the two study groups did not reach levels of statistical significance (p=0.6).

D. Duration of Invasive Ventilation

It was observed that average duration of invasive ventilation requirement in high protein dose group was 1.09 days vs 1.71 days in low protein dose group as shown in Table 5. The comparatively shorter duration of invasive ventilation in high protein dose group vs low protein dose group did not reach levels of statistical significance (p=0.27).

Complications

The complications of prematurity observed for in the study were retinopathy of prematurity, intraventricular hemorrhage, hemodynamically significant patent ductus arteriosus and neonatal necrotising enterocolitis. In this study group, no cases of necrotising enterocolitis occurred. Hemodynamically significant Patent ductus arteriosus requiring medication occurred in 9 babies in each of the study groups. Intraventricular hemorrhage occurred in five babies (15.6%) of the high protein dosage group and in eight babies (28.6%) of the low protein dosage group. Retinopathy of prematurity occurred in seven babies in each of the groups. Their distribution is as shown in the Table 6. There was no significant difference in the incidence of complications of prematurity encountered in both groups.

Table 1: Protein dosage vs gender distribution

Quantity of Protein	Males	Females
1gm	13	15
3gm	18	14

$X^2 = 0.577df = 1 p = 0.448$ NS

Table 1 reveals an equitable gender distribution between the two study groups.

Table 2: Days to regain birth weight in low dose vs high dose protein groups

Group	Days to regain birth weight
3gm	12.91
1gm	13.82

p=0.465

Table 2 reveals a longer duration for the regain of birth weight in the low dose protein group which did not reach levels of statistical significance.

Table 3: Duration of TPN in low dose vs high dose protein groups

Group	Duration of TPN
3gm	7.41
1gm	7.64

p=0.840

Table 3 shows a marginally shorter duration of TPN in the high dose protein group. However this observation is not statistically significant.

Table 4: Duration of non-invasive ventilation in low dose vs high dose protein groups

Group	Duration of Non-Invasive Ventilation
3gm	5.91
1gm	5.04

p=0.637

Table 4 shows a marginally longer duration of non-invasive ventilation in the high dose protein group.

Table 5: Duration of invasive ventilation in low dose vs high dose protein groups

Group	Duration of Invasive Ventilation
3gm	1.09
1gm	1.71

P=0.271

Table 5 shows a marginally longer duration of invasive ventilation in the low dose protein group.

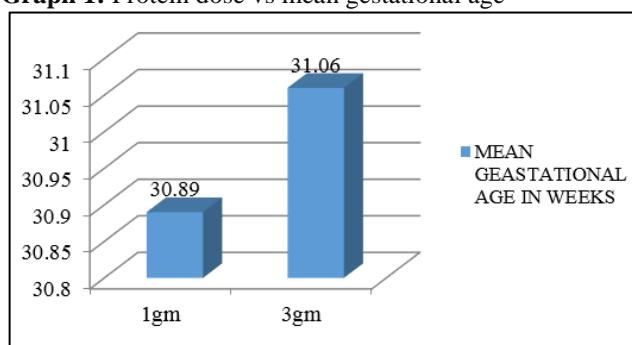
Table 6: Incidence of complications in low vs high dose protein groups

S. No	Complications	Low protein group	High protein group	P value
1	HS PDA	9	9	0.73 (NS)
2	IVH	8	5	0.22 (NS)
3	ROP	7	7	0.77 (NS)

Table 6 shows complications were comparable with regards HS PDA and ROP. IVH occurred more commonly in the low dose protein group.

Graph 1 shows mean gestational age in both the study groups are well matched.

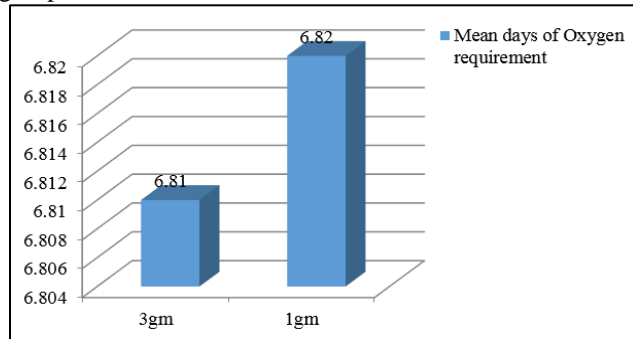
Graph 1: Protein dose vs mean gestational age



p=0.794 NS

Graph 2 shows oxygen dependency duration in both the study groups are comparable.

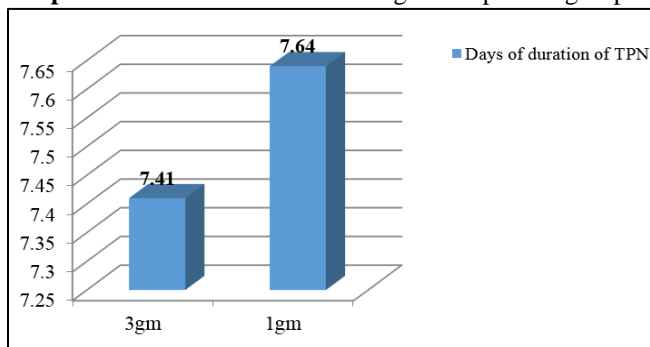
Graph 2: Oxygen dependency in low vs high dose protein groups



p=0.996

Graph 3 shows duration of PN requirement in high dose vs low dose protein groups.

Graph 3: TPN duration in low vs high dose protein groups



p = 0.840

Discussion

Management of the premature infants represents a medical challenge. Achieving adequate nutrition accretion keeping in mind the physiological immaturity in nutrition assimilation is a daunting task. Ensuring optimum nutrition after birth in the small premature neonate is mandatory to ensure not only optimal growth and development but also facilitate an uneventful recovery to enable the baby to be roomed in with the mother at the earliest. Hence early administration of appropriate nutritional support both enteral and parenteral to achieve optimal growth and development is important. This would enable not only appropriate postnatal growth and development but would more importantly decrease the morbidity and mortality thus enabling better outcomes both immediate and long term.

While providing holistic parenteral nutrition support would be the main stay in preterm babies who cannot imbibe adequate nutrition enterally, the appropriate dosage of each of these nutrients to achieve optimum nutrition accretion is the challenge. There are several studies which have questioned the ideal protein dose in parenteral nutrition in preterm neonates which would enable a positive nitrogen

balance with maximum tolerance.⁷Hence this study was undertaken to analyse the appropriate protein dosage in parenteral nutrition in VLBW preterm neonates which would enable optimum nutrition accretion and be safely tolerated.

During the study period, from September 2015 to September 2017, a total of 1647 newborns were admitted in the NICU. Of these, 729 (44.27%) were preterms and 918 admissions were term babies. Of the babies hospitalised, 84 (5.1%) met the inclusion criteria and were enrolled in the study and 60 neonates completed the study. The gender distribution in our study groups was equitable. The mean gestational age in the low protein dosage group was 30.89 weeks and mean gestational age in high protein dose group was 31.06 weeks (p =0.794). In our study mean birth weight in 1gm group was 1201.21grams and mean birth weight in 3gm group was 1239.09 grams (p =0.386). Our study group with regard to sample size, birth weight, gestational age and gender distribution was similar with study conducted by Balasubramanian, et al.⁸

Primary outcomes studied were duration of oxygen requirement and time to regain birth weight. There was no statistically significant difference between quantity of protein provided and oxygen dependency (p = 0.996). This finding is in concordance with studies of Burattini et al and Tan cooke et al.^{9,10} In 3 gm group average number of days to regain birth weight was 12.91 days and in 1gm group it was 13.82 days. Whilst the time to regain birth group was relatively shorter in high dose protein group it did not reach the levels of statistical significance. This finding is in concordance with other studies.^{11,12}

The secondary outcomes studied were duration of hospital stay, duration of PN and duration of invasive/ non invasive ventilation. Hospital stay duration was 18.69 vs 19.29 days in high dose vs low dose protein groups. Duration of TPN was 7.41 vs 7.64 days in high dose vs low dose protein groups. In the 3 grams protein dose group, average duration of hospital stay was 18.69 days and in 1 gram group it was 19.29 days. There was no statistically significant difference between quantity of proteins provided and days of hospital stay (p = 0.843). Ventilator dependency with regard to both non invasive and invasive ventilation support were comparable in the two groups. These findings are in concordance with other studies.^{8,13}

Complications associated with prematurity studied were hemodynamically significant PDA, Retinopathy of Prematurity, Intra Ventricular Hemorrhage and Necrotizing Enterocolitis. In our study we did not find any cases of NNEC. While there was an increased occurrence of intraventricular hemorrhage in the low dose protein group as compared to the high protein dose group, it did not reach levels of statistical significance. The other complications encountered were comparable. This observation is in concordance with other studies.^{8,13}

Conclusions

This study suggests that low dose protein administration in parenteral nutrition is as efficacious as high dose protein

dosage in premature neonates. It is also as well tolerated. Whilst there was a marginal benefit of high dose protein therapy in curtailing duration of hospitalization, time to reach full feeds, duration of respiratory support and incidence of intraventricular haemorrhage, this did not reach the levels of statistical significance. The relatively small sample size was the limitation in the study. Large scale studies involving several centers would perhaps substantiate more effectively the appropriate dose of proteins which would enable optimum nutrition accretion and be well tolerated in parenteral nutrition therapy in very low birth weight preterm neonates.

Conflict of Interest: None.

References

- Hulst JM, van Goudoever JB, Zimmermann LJ, Hop WC, Albers MJ, Tibboel D et al. The effect of cumulative energy and protein deficiency on anthropometric parameters in a pediatric ICU population. *Clin Nutr* 2004;23:1381-9.
- Prado EL, Dewey KG: Nutrition and brain development in early life. *Nutr Rev* 2014;72:267–84.
- Porcelli PJ Jr, Sisk PM: Increased parenteral amino acid administration to extremely low birth-weight infants during early postnatal life. *J Pediatr Gastroenterol Nutr* 2002;34:174–9.
- Can E, Bulbul A, Uslu S, Comert S, Bolat F, Nuhoglu A. Effects of aggressive parenteral nutrition on growth and clinical outcome in preterm infants. *Pediatr Int* 2012;54:869–74.
- Te Braake FW, Schierbeek H, de Groof K, Vermes A, Longini M, Buonocore G, vanGoudoever JB. Glutathione synthesis rates after amino acid administration directly after birth in preterm infants. *Am J Clin Nutr* 2008;88:333–9.
- 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. *J Pediatr* 2013;163:638–44.e5.
- Clark RH, Chace DH, Spitzer AR. 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 randomized, controlled trial. *Pediatr* 2007;120:1286-96.
- Balasubramanian H, Nanavati R, Kabra N. Effect of two different doses of parenteral amino acid supplementation on postnatal growth of very low birth weight neonates — A randomized controlled trial. *Indian Pediatr* 2013;50(12):1131-6.
- Burattini I, Bellagamba MP, Spagnoli C, D'Ascenzo R, Mazzoni N, Peretti A, Cogo PE, Carnielli VP. Targeting 2.5 versus 4 g/kg/day of amino acids for extremely low birth weight infants: a randomized clinical trial. *J Pediatr* 2013;163:1278–82.e1.
- Tan MJ, Cooke RW. Improving head growth in very preterm infants – a randomised controlled trial I: neonatal outcomes. *Arch Dis Child* 2008;93:F337–F341.
- Bellagamba MP, Carmenati E, D'Ascenzo R, Malatesta M, Spagnoli C, Biagetti C, Burattini I, Carnielli VP. One extra gram of protein to preterm infants from birth to 1,800 g: a singleblinded randomized clinical trial. *J Pediatr Gastroenterol Nutr* 2016;62:879–84.
- Scattolin S, Gaio P, Betto M, Palatron S, De Terlizzi F, Intini F, Visintin G, Verlato G: Parenteral amino acid intakes: possible influences of higher intakes on growth and bone status in preterm infants. *J Perinatol* 2013;33:33–9.
- Trivedi A Sinn J. Early versus late administration of amino acids in preterm infants receiving parenteral nutrition. *Cochrane Database of Systematic Reviews*. 2010.

How to cite this article: Kumar MS, Reddy AA, Reddy MP, Boda S, Raju U. A comparative study of low dose (1gm/Kg/Day) vs high dose (3gm/kg/day) protein parenteral nutrition therapy on nutrition accretion and outcomes in very low birth weight preterm neonates- a randomized controlled trial. *Int J Med Paediatr Oncol* 2019;5(2):69-73.