RANDOMISED CONTROLLED TRIAL OF AGGRESSIVE VS SLOW GRADING UP OF TOTAL PARENTERAL NUTRITION IN PRETERM NEONATES

A dissertation submitted to the Tamilnadu Dr. M.G.R. Medical University in partial fulfillment of the University regulations for the award of D.M. (Branch – XI) (Neonatology).

AUGUST 2014

RANDOMISED CONTROLLED TRIAL OF AGGRESSIVE VS SLOW GRADING UP OF TOTAL PARENTERAL NUTRITION IN PRETERM NEONATES

DOCTORATE IN MEDICINE (NEONATOLOGY)

OF

DR. BINU GOVIND

DEPARTMENT OF NEONATOLOGY

CHRISTIAN MEDICAL COLLEGE

VELLORE – 632 004

Certification

This is to certify that the dissertation entitled "**RANDOMISED CONTROLLED TRIAL COMPARING AGGRESSIVE VS SLOW GRADING UP OF TOTAL PARENTERAL NUTRITION IN NEONATES**" is a bonafide original work done by **Dr. Binu Govind** in the Department of Neonatology, Christian Medical College, Vellore in partial fulfilment of the Tamil Nadu Dr. M.G.R. Medical University for award of **Doctorate in Medicine (branch XI) Neonatology**, under my guidance and supervision during the academic year 2011-2014.

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Sub: **Fluid Research grant project NEW PROPOSAL**
Randomized controlled trial of aggressive vs. slow grading up of total parenteral nutrition in preterm neonates.
Dr. Binu Govind, Employment no:32325, PG Registrar, Neonatology, Dr. K. Anil Kuruvilla, Employment no;12469, Dr. S. Sridhar, Employment No 30531, Neonatology

Ref: IRB Min. No. 8304 [INTERVEN] dated 24.04.2013

Dear Dr. Binu Govind,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Randomized controlled trial of aggressive vs. slow grading up of total parenteral nutrition in preterm neonates " on April 24, 2013.

The Committee reviewed the following documents:

1. Format for application to IRB submission
2. Information Sheet and Informed Consent Form (English, Tamil and Telugu)
3. Proforma
4. Cvs of Drs. Binu Govind, K. Anil Kuruvilla, S. Sridhar.
5. A CD containing documents 1 - 4

The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on April 24, 2013 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent. And on completion of the study you are expected to submit a copy of the final report.

A sum of Rs. 40,000/- (Rupees Forty Thousand only) will be granted for 1 year.

Yours sincerely,

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3

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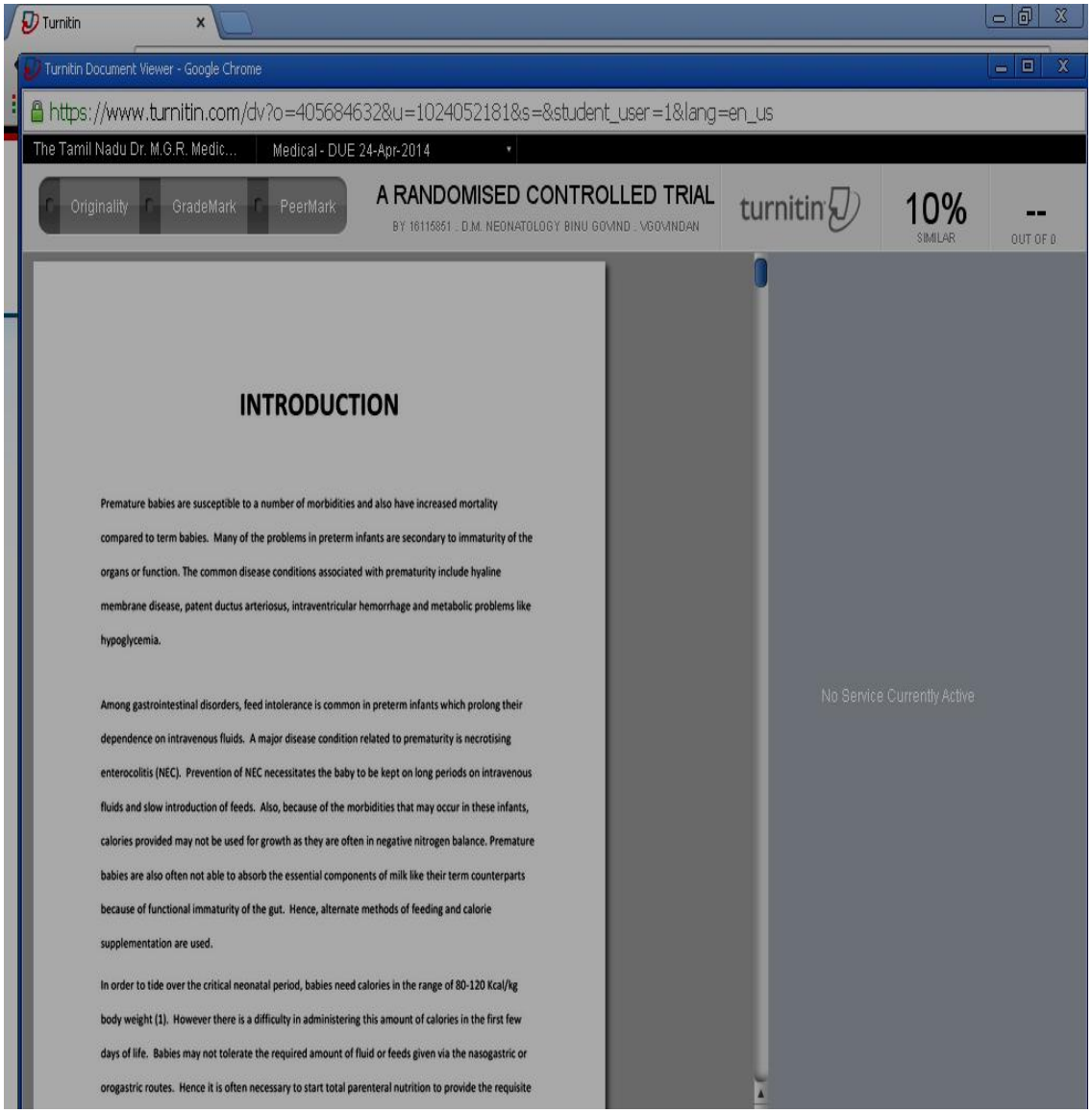
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INTRODUCTION
Premature babies are susceptible to a number of morbidities and also have increased mortality compared to term babies. Many of the problems in preterm infants are secondary to immaturity of the organs or function. The common disease conditions associated with prematurity include hyaline membrane disease, patent ductus arteriosus, intraventricular hemorrhage and metabolic problems like hypoglycemia.
Among gastrointestinal disorders, feed intolerance is common in preterm infants which prolong their dependence on intravenous fluids. A major disease condition related to prematurity is necrotising enterocolitis (NEC). Prevention of NEC necessitates the baby to be kept on long periods on intravenous fluids and slow introduction of feeds. Also, because of the morbidities that may occur in these infants, calories provided may not be used for growth as they are often in negative nitrogen balance. Premature babies are also often not able to absorb the essential components of milk like their term counterparts because of functional immaturity of the gut. Hence, alternate methods of feeding and calorie supplementation are used.
In order to tide over the critical neonatal period, babies need calories in the range of 80-120 Kcal/kg body weight (1). However there is a difficulty in administering this amount of calories in the first few days of life. Babies may not tolerate the required amount of fluid or feeds given via the nasogastric or orogastric routes. Hence it is often necessary to start total parenteral nutrition to provide the requisite
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Acknowledgement

Firstly I express my gratitude to God Almighty for his grace and faithfulness.

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Finally I would like to express my appreciation to my wife and family members for their support, encouragement and prayers during these years.

CONTENTS

ABSTRACT

1. **Title**: Randomised controlled trial comparing aggressive vs slow grading up of total parenteral nutrition in preterm neonates.
2. **Department**: Department of Neonatology, Christian Medical College, Vellore.
3. **Name of the Candidate**: Binu Govind
4. **Degree and Subject**: DM Neonatology
5. **Name of Guide**: Dr. Kurien Anil Kuruvilla
6. **Word Count: 499**

7. **Background:** Premature babies are not able to absorb the essential components of milk like their term counterparts because of immaturity of the gut. Hence, total parenteral nutrition is provided to meet their requirements. It is important to determine whether preterm babies can tolerate high amounts of lipid and amino acid from day 1 to improve the nutrition and whether the benefits outweigh the risks.

8. Objective: To compare the differences in the determinants of growth (weight, length and head circumference) following aggressive vs standard (slow grading up) TPN in preterm babies.

9. Setting: Tertiary care perinatal centre in south India

10. Methods: This was a double blind randomised control trial where preterm babies ≤1300g were given aggressive or standard TPN. Aggressive TPN group was started on 3.5g/kg of amino acid and 3 g/kg of lipid from day 1 of life. Standard TPN group was started on 1 g/kg of amino acid from day 1 and 1g/kg of lipid from day 2 of life; increasing by 0.5g/kg to a maximum of 3.5g/kg of amino acid and 3 g/kg of lipid over a period of 5-6 days. The two groups were compared for differences in gain in weight, length, head

circumference; morbidity patterns, metabolic abnormalities, time to reach adequate enteral feeds and regain birth weight.

11. Results: Babies in the aggressive TPN group gained more weight compared to the standard group but the difference in rate of growth was not statistically significant (mean (SD) 10.06 (4.11) vs 9.61(3.91),p=0.66). Similarly, the gain in length and head circumference was also higher in the aggressive group (length in cm/week: 1.11(0.55) vs 0.98(0.62),p=0.40; head circumference in cm/week (0.80(0.19) vs 0.79(0.23),p=0.82). The time to regain birth weight was more in the standard group (14(5.62) vs 12.53(4.31), p=0.26) compared to the aggressive group. The time to reach nasogastric feeds of 100ml/kg/day was longer in the aggressive group, but the difference was not statistically significant (11.73 (4.60) vs 10.79 (3.86), p= 0.60). The duration of TPN administration was comparable between the aggressive and standard groups (7.86 (5.67) vs 7.57(3.33),p=0.75).

12. Conclusion: Providing increased amounts of amino acid and lipid from day one showed a trend towards a positive effect on weight, length and head circumference when compared to the standard method of TPN administration in preterm babies ≤1300g. However the difference did not reach statistical significance in this study. The number of days needed to attain full nasogastric feeds was longer in the aggressive group and days to regain birth weight was less in the aggressive group but the differences were not statistically significant. There was no significant difference in the morbidities and metabolic problems in babies in the aggressive and standard TPN groups.

INTRODUCTION

Premature babies are susceptible to a number of morbidities and also have increased mortality compared to term babies. Many of the problems in preterm infants are secondary to immaturity of the organs or function. The common disease conditions associated with prematurity include hyaline membrane disease, patent ductus arteriosus, intraventricular hemorrhage and metabolic problems like hypoglycemia.

Among gastrointestinal disorders, feed intolerance is common in preterm infants which prolong their dependence on intravenous fluids. A major disease condition related to prematurity is necrotising enterocolitis (NEC). Prevention of NEC necessitates the baby to be kept on intravenous fluids for long periods with slow introduction of feeds. Also, because of the morbidities that may occur in these infants, calories provided may not be used for growth as they are often in negative nitrogen balance. Premature babies are also often not able to absorb the essential components of milk like their term counterparts because of functional immaturity of the gut. Hence, alternate methods of feeding and calorie supplementation are used.

In order to tide over the critical neonatal period, babies need calories in the range of 80-120 Kcal/kg body weight (1). However there is a difficulty in administering this amount of calories in the first few days of life. Babies may not tolerate the required amount of fluid or feeds given via the nasogastric or orogastric routes. Hence it is often necessary to start total parenteral nutrition to provide the requisite calories.

The importance of proper nutrition and the effect of nutrition on long term neurodevelopmental outcome have been studied. Early adequate nutrition in preterm babies can improve neurodevelopmental outcome (2). Studies correlating the growth of head with adequate nutrition in VLBW babies suggest that head growth proportionately increases in response to added calories. It is currently recommended that amino acids and lipids be given early in life to provide adequate calories (1). The amount of amino acids and lipids babies can tolerate and how fast this is to be administered has also been studied and guidelines have been developed regarding total parenteral nutrition (TPN) in VLBW babies (1). The various components of lipid and amino acid preparations which are essential for the baby is also important.

Currently the standard practice in our hospital has been to give amino acids and lipid over a period of 1 week. Few studies have attempted to give high amounts of lipid and amino acid from day 1. It is important to determine whether our babies can tolerate high amounts of lipid and amino acid from day 1 and whether the benefits outweigh the risks.

AIMS AND OBJECTIVES

Aim

To compare the differences in the determinants of growth (weight, length and head circumference) following aggressive versus the standard regimen (slow grading up) of total parenteral nutrition (TPN) in preterm babies.

Objectives

Primary Objective

To compare the differences in the determinants of growth (weight, length and head circumference) following aggressive and standard (slow grading up) of TPN at the end of 28 days.

Secondary Objective

Compare babies receiving aggressive versus standard TPN in

-time taken to regain birth weight

-time to reach full nasogastric feeds

-effect on common morbidities of prematurity, e.g. feed intolerance, necrotizing enterocolitis, sepsis, respiratory distress, intraventricular hemorrhage, patent ductus arteriosus, cholestasis.

REVIEW OF LITERATURE

Preterm babies often receive lesser amounts of calories in the first few weeks of life. As a result, many nutritional deficiencies may develop in the neonatal period which affects growth of the baby in the long term. It is estimated that 80-120 Kcal/kg is required for postnatal growth in the initial weeks of life (1). It may not be possible to give this quantity in the early days of life, especially in preterm infants. Also, there are often other morbidities in these babies which may necessitate increased energy intake. Very low birth weight (VLBW) preterm babies also have an immature gut that cannot digest food given as milk in adequate quantities. Hence it is often necessary to give nutrition intravenously in the form amino acids, lipid and dextrose to give adequate calories for growth (1).

Babies born at term usually gain weight with breast feeding and there is a smooth transition from intrauterine life. Intrauterine accretion occurs maximally in the last trimester, so preterm babies born early have a deficiency in this aspect. Immaturity of the gut in preterm babies makes it difficult for them to digest adequate quantities of milk. Hence we need to give total parenteral nutrition (TPN) to babies to maintain growth.

A preterm baby who has no protein supplementation as part of the TPN will be in a catabolic state. There could be break down of body proteins at a rate of 1-1.5g/kg/day (1). In addition to the importance of the last trimester in intrauterine accretion, it is also a period where neuronal development occurs in the form of myelination and dendritic arborization. Babies who receive inadequate nutrition in the immediate postnatal period have been found to have a higher incidence of neurodevelopmental delay and cerebral palsy (2).

Hence it is important to provide the necessary calories and various components of nutrition to optimize growth. The importance of giving adequate TPN and its effect on physical

parameters like weight, length and head circumference needs further study, along with tolerance levels.

Energy requirements and growth

Ehrenkranz et al has plotted growth curves for weight, height and head circumference for very low birth weight babies and has opined that the various nutritional interventions which are beneficial should be plotted against the graph and compared (3). He also proposed that growth velocity in the newborn period has a role to play in the neurodevelopmental outcome. The faster the growth of the baby, the better were the MDI, PDI scores and lesser was the incidence of cerebral palsy (2). This reinforces the fact that the earlier proper nutrition is given to the baby, it has long term beneficial effects.

Energy needs of a newborn baby are usually considered under four headings - Basal Metabolic Rate (BMR), diet induced thermogenesis, physical activity and growth. Resting Energy Expenditure (REE) is used to calculate the energy requirements of the newborn. Open circuit indirect calorimetry is the method commonly used to measure the Resting Energy requirement.

Resting Energy Expenditure (Schofield formula) = 59.48x Wt; REE is 30.33 in males and 58.29xWt-31.05 in females.

Energy intake of 110-120 Kcals/kg/body wt will facilitate growth in ELBW babies(1). Protein accretion starts when the calorie intake exceeds 70Kcals/kg body wt. Protein-Energy ratio required to achieve fetal growth is maximum in very premature babies. Non-protein energy in the form of carbohydrates and fat are needed in adequate amounts to prevent body proteins being catabolised. There should be an adequate balance between nitrogen and non-nitrogen sources of energy.

Energy Requirement= Energy expended+ Energy stored+ Energy excreted

Energy is expended for basal metabolism, thermoregulation, activity and growth.

Table 1

Energy Expended	Kcals/kg/day
Basal metabolism	40-60
Activity	0-5
Thermoregulation	0-5
Growth	15
Energy excreted	15
Energy stored	20-30
Total Requirement	90-120

A study conducted by Bauer et al evaluated oxygen consumption, energy expenditure and carbon dioxide production in ELBW infants to ascertain energy requirements and metabolism of babies (4). They ascertained that energy expenditure values were related to energy intake and weight gain and were not dependent on postnatal age. Bauer et al measured energy expenditure longitudinally in healthy preterm and term infants and have derived reference values for comparison (5). The derived values may have to be interpreted with caution in sick babies. It is well known that the various disease conditions of prematurity increase the energy requirement in sick babies so energy intake may have to be increased accordingly.

Berry et al conducted a study to determine the factors associated with growth retardation in small babies and evaluated that respiratory support and steroid usage may affect growth (6). He postulated that proper calorie and protein supply may potentiate growth but it was difficult to attain the recommended dosage. Most sick babies may not be able to tolerate the amount of fluid input needed to supply the required calories.

Embleton et al. feels that the current recommendations for nutrition are insufficient and it is a contributory factor for growth retardation (7).

Calories have to be provided in adequate amounts for efficient growth. A minimal calorie intake of 40-50 Kals/kg/day is needed so that the proteins may be utilized for the growth of the baby. Optimal utilisation of proteins is necessary for adequate growth. Nitrogen intake was mostly dependent on protein intake when the energy consumed exceeded 70Kcals/kg/day in newborns.

Zlotkin et al has studied the relationship between nitrogen intake and nitrogen retention and found out that at energy intake of greater than 70Kcals/kg/day, nitrogen accretion was determined by the amount of nitrogen intake (8).

A Protein/Energy ratio of 3-4g/100Kcals is ideally preferred for efficient protein accumulation. Kashyap et al has stressed on the amount of protein, energy and fat that can be given to babies and also the protein/energy ratio that should be targeted in these babies (9). Ideally, it would be preferable to have about 55-70% of non-protein calories from carbohydrate and 25-40% of the required calories from lipids. A ratio of 50-55% carbohydrate, 10-15% proteins and 30-35% from fats is optimum.

The utilization of amino acid depends on sufficient energy intake of 30-40Kcals/1g of amino acid. If calories can be provided in the above mentioned amounts, the protein administered can be utilized for tissue growth. Protein should only be utilized for tissue growth and lipid

and carbohydrate should be provided to prevent catabolism of tissue (2). In a thermoneutral environment, an intake of 50Kcals/kg/day is needed to maintain ongoing energy expenditure. The estimated intrauterine accretion rate in fetus is about 14-15g/kg/day. An additional 70Kcals/kg/day is needed to maintain intrauterine accretion rate. The energy needed for attaining 1g of new tissue is ~5 KCal (3).

The calorie content of 10% Dextrose is 0.34Kcals/ml (3.4 Kcal/g), 20% lipid is 2Kcals/ml (10 Kcal/g) and 10% amino acid is 0.4kcals/ml (4 Kcal/g).

Clark et al postulated that proper early administration of TPN in addition to early enteral nutrition helps in better weight gain (10). However factors that can contribute to adverse conditions such as NEC have to also be looked into. Babies for whom early nutrition was started parenterally along with minimal enteral nutrition were noted to have better weight gain with regaining of birth weight faster.

Poindexter et al showed that growth failure is very common in the newborn period. 40% of the extremely low birth weight babies(<1kg) who were followed up at 18 months were noted to have lower birth weight, length and head circumference less than the 10^{th} centile after receiving the standard neonatal care (total parenteral nutrition along with grading up of orogastric feed) based on data available at NICHD (11). They have suggested that since aggressive parenteral nutrition was tolerated well in these babies, it is better to start early nutrition support in these babies for the best results possible.

Crighton et al noted that higher carbohydrate can be given to babies without the possibility of high CO_2 production. They do tolerate it well and total calorie content can be improved (12). However there are limits to which we can increase carbohydrate content so the role of TPN becomes important.

Calorie administration and neurodevelopmental outcome

Head growth is an important measure of growth failure as it correlates with brain growth. There are various studies which show that adequate nutrition increased brain growth with corresponding increase in developmental scores later. Cooke et al studied 485 fetuses and concluded that babies with larger head circumference had larger brains (13). Cooke et al also postulated that tests of motor impairment correlated strongly with occipitofrontal circumference at discharge. He noted that the smaller the head circumference, the greater was the motor impairment. He suggested that the tests also correlated positively with the rate of growth of head from birth to the day of discharge. The faster the head grew in the initial days of life, the better was the motor development (14). Georgieff et al also mentions that calorie deprived infants had head growth which was 1 SD less than normal after about 4 weeks of life, and also had developmental scores less than normal at 1 year of life (15).

Hack et al proposed that very low birth weight babies who were not given proper nutrition in the newborn period had probably subnormal head circumference at 8 months of life (16). These babies also had poor neurodevelopmental scores.

Tan et al has postulated that if proper nutrition was given in the newborn period , brain growth was facilitated (17). Tan et al evaluated babies born <29 weeks of gestation and compared two groups-hyperalimentation and standard feeding. In the hyperalimentation group the targeted energy intake was 133-150 Kcal/kg/day and 4g/kg/day of protein and lipid; it was gradually graded up over 4-5 days .However, in the control group targeted energy was 133 kcal/kg/day and 3g/kg/day of protein and lipid each graded over 4-5 days Babies in the intervention group received more energy (mean diff 144kcals/kg 95%CI 56-232 kcals/kg, $p<0.01$) and protein (mean diff 9g/kg,95%CI 7-12g/kg, $p<0.001$). A correlation between protein and energy deficit (in the first 28 days of life) and lower head growth at 36 weeks

corrected gestational age was demonstrated. It was also reported that increase in growth of the brain as shown by MRI did correlate positively with the later developmental outcome.

Amino acid

The value of giving amino acid as a part of parenteral nutrition has been dealt with in detail over the years. Aminoacid can be given from birth. They include 9 essential (Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Threonine, Tryptophan and Valine) and 5 conditionally essential aminoacid (Arginine, Cysteine, Glycine , Proline and Tyrosine). These amino acids should be included in TPN solutions as they may not be synthesized efficiently in sick babies (1). Requirements for various amino acid may be calculated based on amino acid indicator method.

A newborn baby will catabolise around 1g/kg/day of its protein if calories are not provided in adequate amounts. A minimum amount of 1-1.5g/kg/day of amino acid needs to be given to preterm babies on day 1 to avoid negative protein balance. It has also been noted that starting amino acids at 3 g/kg/day soon after birth has not been associated with adverse effects (1). The protein requirements for smaller preterms are more than that for term babies. The dosage recommended include a maximum of 3-4 g/kg/day in preterms and 3g/kg/day in term babies (1, 2)

Current amino acid preparations available for neonates are based on the plasma aminograms of either cord blood or breast fed term infants (10). 10%aminoven is the amino acid currently used in our nursery.

Chessex et al found that serum values of amino acid and nitrogen retention of babies was dependent on the amino acid preparation given to the baby (18). A higher dose of amino acid resulted in a higher nitrogen retention. He could not identify any adverse effects on starting

amino acid early. This was reinforced by Clarke et al, but they cautioned the possibility of metabolic imbalance in babies secondary to the increased protein (19).

There are concerns on whether the ELBW babies are able to metabolize effectively the amino acid preparations in parenteral fluid. Clarke et al found that leucine oxidation increased with added leucine but there was a limit in phenylalanine oxidation in preterms (20). However Denne et al could not identify any limitation in the utilisation of phenylalanine by preterms but he noted that proteolysis could not be reduced much by protein supplementation in VLBW babies (21).

The ideal amino acid compositions that can be given to small babies have been a matter of debate. It would be prudent to know which amino acids could be metabolized by an ELBW baby. Heird et al tried to identify the amino acid concentration in babies in TPN and has put forward suggestions on amino acid composition (22). He has advised taurine supplementation along with routine amino acid supplementation. Heird et al also studied the efficacy of utilisation of amino acids in LBW infants; in a study on 28 infants they concluded that the ability of LBW babies to utilize tyrosine and cystine was less, but not as low as thought previously (23).

Amino acid administration and adverse events

It is important to know how much amount of amino acids each baby can tolerate. Kashyap et al studied the effects of 3 gradients of protein and energy intake in 3 sets of newborn. It was found out that protein accretion was higher in the higher protein intake group, but energy expenditure was also higher in this group, possibly due to the energy expended to metabolize the higher protein (24). Also, the ratio of protein to fat accretion reflected the intake of protein and fat respectively (25). Poindexter evaluated the difference between early and late administration of amino acids and looked at growth parameters (26, 27). He found that

supplementation of amino acid at an early age improved the growth of the baby at 36 weeks corrected age and this also had a positive influence on head circumference.

The effect of protein supplementation in the parenteral fluid and the effect on metabolic parameters was also studied. The effect of protein supplementation on metabolic acidosis and blood urea were seen. It was seen that upto 4g/kg/day of protein was tolerated without metabolic acidosis (28). Also it was noted that blood urea levels correlated poorly with protein intake and restricting protein intake based on urea levels may not be prudent (29).

Rivera et al evaluated protein tolerance of ELBW babies by giving 1.5g/kg/day from day 1 of life. He noted that these babies had better nitrogen retention, leucine oxidation and protein synthesis than the control group (30). Other studies also advocated early supplementation of amino acids without the possibility of adverse events (31,32).

Thureen et al compared high doses (3g/kg) versus low (1g/kg) doses of amino acid in ELBW babies; tolerance levels were similar without any adverse effect. There was increased protein accretion with increased synthesis (33).

There are various studies which reinforced the importance of early administration of amino acid and found that this is associated with better weight and lesser metabolic imbalance (34-37). This has currently led to the consensus on early supplementation of amino acids (1).

Lipid

There are two roles for lipids as part of TPN – as a source of Essential fatty acids (EFA) and as an energy source. Lipids should provide 40% of the nonprotein calorie in newborn. Lipids are a good source of energy with less osmolarity and carbon dioxide production so can be given safely and even through a peripheral vein. Lipid administration should be optimized so that excess of carbohydrate intake for energy can be avoided and other side effects like carbon dioxide production can be minimized.

Lipid preparations are of three types- Soy bean based, Olive oil based and fish oil based emulsions. They give the necessary triglycerides which are metabolized by lipoprotein lipase into free fatty acids. Soy bean preparation also gives the necessary EFA (linoleic -omega6 and linolenic acid- omega 3) with a minimum intake of 0.5-1g/kg/day of lipid .Soy bean based emulsions also contain egg phospholipids (for emulsification) and glycerol (for tonicity). Combination Soy bean (omega6)/olive oil (omega 9) based emulsions contain lesser polyunsaturated fatty acid compared with Soy bean based emulsions alone. However they have improved Vitamin E status and increased long chain triglycerides (LCT) (1). Recently fish oil based lipid preparations (high omega 3) have also come into use. Combinations of Soy, Olive, Fish oil with MCT (eg SMOF) are being evaluated in preterm babies.

Standard 20% emulsions contain lower ratio of phospholipid emulsifier / triglyceride. So there is better mobilization of triglycerides for energy. Hence 20% emulsions are preferred over 10% emulsions for lipid administration. A minimum Linoleic acid intake of 0.25g/kg/day should be given to preterms.

Lipids are usually administered wrapped in aluminium foils as exposure to light may cause lipid peroxidation. Lipids may be combined with fat soluble vitamins to minimize peroxidation.

Dosage of lipids is usually limited to a maximum of 3-4 g/kg/day. Lipid infusion can be started at 1g/kg/day on day2 and graded up by 0.5g/kg/day to a maximum of 3 g/kg/day (4)

Lipid administration and adverse events

The possibility of increased Oxygen requirements has necessitated the infusion of lipid to be curtailed to a maximum of 0.15g/kg/hour. The theoretical possibility of bilirubin displacement from albumin necessitates precaution in severe jaundice (9).

In cases of severe thrombocytopenia, serum triglyceride concentration (<250mg/dl) should be checked and reduction in dosage considered, as lipid can interfere with platelet aggregation. Carnitine supplementation should be considered if TPN is given >4 weeks.

If serum triglyceride concentration exceeds 250 mg/dl, lipid emulsion should be suspended and restarted at 0.5-2g/kg/day (1)

The introduction of lipid in ELBW babies from day 1 of life is now currently recommended. There are various studies outlining the importance of early administration of lipid to make up the calorie requirement.

There are concerns about the effect of lipid administration on bilirubin levels in small babies. Amin et al administered 1,1.5,2,2.5 and 3g/kg intralipid in 24-33 weeks gestational age babies and noted that the amount of free bilirubin is increased depending on the amount of intralipid administered (38). It was mentioned that the ratio of free fatty acid to bilirubin may be more important and when the ratio of free fatty acid to bilirubin exceeds 6, there is a possibility of bilirubin displacement (39). Hence it is recommended to monitor the bilirubin levels during TPN administration if there is clinical jaundice.

Basu et al hypothesized that free radical formation could occur with fat supplementation but by promoting fat utilisation by reducing the carbohydrate/fat ratio, it can be minimised (40).

The amount of lipid that a newborn tolerates is also under study especially whether small ELBW babies can tolerate increased amounts of lipid. Brans et al noted that when lipids are given at various infusion rates, the serum concentration of lipid was dependent on the hourly infusion rate and not on the total amount (41). He also noted that babies did tolerate upto 4g/kg/day of lipid without any worsening of oxygenation.

Gilbertson compared lipid administration from day1 to later administration and has opined that babies do tolerate lipid administration on day 1 provided the lipid infusion does not exceed 0.15g/kg/hr (42).

Hilliard et al found out that the lipid fractions in the blood increased till 2g/kg/day and thereafter remained constant even at infusions of 4g/kg/day (43). However, the tolerance of the baby to continuous infusion of TPN when compared with intermittent TPN and which is more suitable has to be looked into. Kao et al compared intermittent (8 hrs) vs continuous (24hrs) intralipid administration and showed that preterms tolerated continuous infusion better(44)

Hageman has also opined that lipid infusion does not interfere with ventilation and non pulmonary factors may be the cause (45) but this is contrary to the other studies (46)(47). Lipid administration is to be used with caution in ventilated sick babies because of increased oxygen requirements and presence of lipid peroxide formation may cause additional problems (46)(47). Sosenko et al could not find any positive effects on ventilation with lipid administration (48) and various studies reported earlier showed that oxygen requirement may increase.

Haumont et al compared 10% vs 20% intralipid administration and came to the conclusion that higher phospholipids in the 10% solution may be the cause of higher triglycerides, cholesterol and phospholipids, so 20% intralipids may be preferable (49). The various components of lipid preparation currently available in the market have to be looked into. Putet et al has listed the various categories of lipid preparations available and marked their components also (50).

Stahl et al described in detail the steps of lipid metabolism in a VLBW baby (51) which are essential in a small baby and will help us to understand how much of lipid they can tolerate.

Spear et al has suggested that heparin administration to a lipid level of 2g/kg/day helps to keep the free fatty acid concentration to a reasonable level (52) but this was in contrary to the earlier mentioned study (53).

Simmer et al did a review on early introduction of lipid and came to the conclusion that early introduction of lipid may not have any statistical significance regarding the growth of babies (54).

There have been concerns about adverse events in case of lipid administration. Campbell has reported a case of bleeding following intralipid infusion (55). It was postulated that there were alteration of platelet function secondary to lipid administration. It has been suggested that serum lipid levels be measured along with coagulation parameters to know the safety of lipid administration and to reduce the lipid infusion if necessary (56-59) .

There have been reports of cholestasis as a problem with intralipid infusion and so reduction in the amount of lipid may be necessary to tide over the crises (60)(61) . It was suggested that it may be prudent to stop lipid for 72 hrs and reintroduce slowly.

There is some evidence on the association of staphylococcal infection with lipid infusions that emphasizes the importance of aseptic precautions (62)(63).

There have also been reports of lipid administration associated with hyperactivation of the monocyte macrophage system (58).

Grading up of TPN

Newborn babies are given slow grading up of amino acid and lipid along with 10%dextrose as a matter of routine for the past several years. However, how early can we start giving TPN, how much and how fast we can increase it is a matter of debate. It has now become common practice to start total parenteral nutrition from day 1. There have been no reports of adverse

effects following early start of amino acid from day 1. Babies were also evaluated for metabolic problems secondary to grading up of TPN both rapidly and slowly; their biochemical parameters were found to be normal.

The total amount of amino acid that can be given is also a matter of interest. Various studies have shown that amino acid can be successfully graded up to a total of 3.5g/kg/day (28, 34,64,65). Blanco et al (65) studied the effect of high amino acid on metabolic parameters after administering 2g/kg of amino acids on day 1 in intervention group and grading up by 1g/kg every 24 hours to a maximum of 4g/kg/day**.** He started with 0.5g/kg on day 1 in the standard group and graded up by 0.5g/kg/day to a maximum of 3 g/kg/day. Thureen et al (33) evaluated the differences in amount of protein accretion comparing intake of 3g/kg vs. 1g/kg and found out that higher protein intake was associated with better protein accretion and growth. Current recommendations suggest a calorie intake of 80-120Kcals/kg/day and a protein intake in a preterm baby to a maximum of 4g/kg/day (1). The time of starting lipid and grading up has also been studied. Ibrahim et al started lipid from day one at a maximum of 3.5g/kg (64). Both Wilson et al (66) and Murdoch et al(67) started lipid within 24 hrs of life and graded up slowly. Wilson et al (66) compared fast vs slow grading of amino acid and lipid. Mean maximal amino acid intake was 3.5g/kg/day in aggressive vs 2.5g/kg/day in slow group and lipid was administered at a maximum of 3.5g/kg/day in aggressive and 2 g/kg/day in slow group. Gilbertson (42) and Murdoch et al (67) demonstrated good tolerance level to lipids . The total amount of lipid given also varied from 1g (67) to a maximum of 3g/kg/day (64) on day 1 of life. The higher lipid content was well tolerated without any abnormal increase in metabolic parameters.

TPN is often given by slow grading up i.e. by 0.5g-1g/kg/day of amino acid and lipid to a maximum of 3-3.5g/kg/day over a period of 1 week. Some studies have compared this to starting high levels of amino acid and lipid from day 1 onwards (64)(66)(68). Ibrahim et al (64)

looked at short-term factors like tolerability, nitrogen retention, energy intake and weight gain, all of which correlated positively with rapid TPN. Similarly, SCAMP (69) is an ongoing study comparing fast vs slow grading of TPN measuring the primary outcome as head circumference. Morgan et al compared standard (2.8g/kg of protein and lipid each along with 10% dextrose) with aggressive (3.8g/kg of protein and lipid each along with 12%dextrose) in babies<29 weeks of gestation and planned to measure the head circumference at 28 days of age and neurodevelopmental outcome at 2 years of life (69).

Ibrahim et al (64) compared early high parenteral nutrition (3.5g amino acid and 3 g lipids) to low grade of parenteral nutrition (2 g amino acid and 0.5g lipids) from day 1 of life in term in 32 ventilator dependent preterms and opined that nitrogen retention and calorie intake was better in the aggressive group with lesser incidence of metabolic acidosis, hypertriglyceridemia etc ,thus proving that aggressive TPN can be tolerated in small sick preterms (64).

Wilson et al (66) has compared standard TPN with aggressive TPN to look at the effect on common morbidities of prematurity. Their hypothesis was that improving nutrition in the first few days of life may help preterms to better cope with their illness and improve outcome. The results showed that higher energy could be given in the aggressive group without increasing morbidities like bronchopulmonary dysplasia, septicemia, cholestasis and necrotising enterocolitis.

Murdoch et al has stressed on importance of early supplementation of amino acid, lipid and protein in the immediate neonatal period and demonstrated metabolic imbalance in cases of delayed starting of TPN (67).

Dinerstein compared early grading of amino acid to a maximum of 4g/kg and lipid to a maximum of 3.5g/kg over a period of few days and noted that there was better growth as

denoted by weight, head circumference etc in the early graded up group (70). The study was conducted in a cohort of 117 VLBW babies. Thureen et al commented that extreme preterms have an energy storage of around 4 days to maintain energy balance (71). He has advised that early starting of TPN will help in better energy ratio and so it is necessary to start TPN at an early age (72). Wang et al has also opined based on a retrospective study that early starting of TPN is associated with better nutritional estimates (73).

Thus it is likely that rapid TPN and improved nutrition from day 1 may help preterm babies have better postnatal growth, thereby facilitating earlier discharge. This may also play a part in better long term neurological outcome by improving early brain growth. It may be possible that early nutrition may prevent early morbidities of preterm and help them cope better with illness.

RATIONALE FOR THE STUDY

Preterm very low birth weight babies need large amounts of calories to meet requirements and the additional burden posed by various morbidities. The current method of providing total parenteral nutrition (TPN) is by grading up over a period of 5-7 days. However this may not be helpful in giving adequate calories in the initial part of life, when it is most needed the most to tide over the various crises.

It is important to study whether it is possible to safely give increased amounts of TPN from day 1. Also, we need to ensure that the additional amounts are well tolerated without undue metabolic imbalance and survival of babies improves.

This study was designed to compare the conventional method of administering TPN with a more aggressive approach of giving larger amounts of lipid and calories from day 1.

If it is possible to demonstrate that giving aggressive TPN from the first day of birth helps babies to gain weight better with no major adverse effects, this could become the standard of care in the future for preterm infants.

Similarly, if aggressive TPN helps provide better nutrition that helps preterm babies to better cope with their various disease conditions, it can be used as a means of improving outcome in sick preterm infants.

MATERIALS AND METHODS

Design

Randomised double blind controlled study

Setting

The study was conducted in the Department of Neonatology, Christian Medical College, Vellore. The hospital is tertiary care teaching centre in southern India.

All babies of birth weight ≤ 1300 g admitted in the unit were included in the study.

Participants

All babies ≤1300g were recruited in the study if their age was <24 hrs at the time of admission to the nursery.

Key Criteria

Inclusion Criteria:

Preterm babies with birth weight of 1300 g and below.

Exclusion Criteria:

1) Outborn babies admitted after 24 hrs.
2) Infants with major congenital/chromosomal anomaly with associated microcephaly.
3) Lack of parental consent.

4) Critically ill infants who may not survive beyond 24-48 hrs of birth.

Intervention and Comparator agent

Aggressive TPN starting with 3.5 g/kg of amino acid and 3 g/kg of lipid from day 1 of life

vs

Standard regimen of TPN administration starting with 1 g/kg of amino acid from day 1 and 1g/kg of lipid from day 2 of life; increasing by 0.5g/kg to a maximum of 3.5g/kg of amino acid and 3 g/kg of lipid over a period of 5-6 days.

Informed Consent

Informed consent was taken from the parent if the baby satisfied the inclusion criteria.

Ethics clearance

The study was cleared by the Institutional Review Board and Ethics committee.

Method details

Preterm babies with birth weight <1500g are usually admitted to Level III nursery for intensive care. Of these babies, those ≤1300g meeting the inclusion criteria were enrolled. After obtaining informed written consent from the parents, babies were randomly allocated to receive either the standard TPN regimen or aggressive TPN. Randomization was done using serially numbered opaque sealed envelopes.

Aggressive TPN

The aggressive TPN group was given 3.5g/kg of amino acid and 3 g/kg lipid each along with 10% dextrose (8-10 g/kg/day). This was commenced within 24 hours of birth.

Standard TPN

Babies in the standard TPN group were started on 1g/kg of amino acid on day one and 1 g/kg/day of lipid on day 2, along with 10% dextrose (8-10 g/kg/day). Amino acids and lipids in this group were increased by 0.5 g/kg/day till 3.5 g/kg/day of amino acids and 3 g/kg/day of lipids was achieved.

Route: Babies in both groups were given TPN via an umbilical or percutaneous long line.

Duration: TPN was continued until 100ml/kg of enteral feeds was reached.

Monitoring: The tolerance to TPN was monitored using lab parameters as shown in Table 8-11: Hb, TC,DC, Platelets (day 1 &7), lipid profile (day 7,28), Na, K (day 3,7,14,28), urea, creatinine (day 3,7,14,28), arterial blood gas (day 3), LFT(day 7,28). Lipid profile sample on day 7 was obtained before TPN was started for the day.

Head circumference (bi-weekly), body weight (daily) and length (weekly) was monitored. We also assessed the two groups in terms of time to regain birth weight and pre-specified morbidities that may have occurred.

Table 2: Monitoring Of Parameters

Physical Parameters

Weight	Daily
Length	Weekly
Head circumference	At 24 hours & bi weekly

Blood Parameters

	1	3	7	14	28
Hb, TC, DC, Platelets	√		√		
Arterial blood gas		√			
Na, K Urea, Creatinine		√	√	√	√
Liver function test			√		√
HDL, LDL, Triglycerides			√		√

Target Sample size and rationale:

A sample size of 64 in each group has a 80% power to detect a difference between the means of two ways of TPN administration for the outcome of head growth velocity over the first 28 days after birth of 6 mm. This assumes that the common standard deviation is 12 mm. Sample size of 64 in each arm was calculated by $n=SD^2(Z\alpha+Z\beta)^2/d^2 = 64$.

Method of randomization:

Block randomization of sizes 2,4 or 6 using SAS 9.2.1

Method of allocation concealment

Sealed opaque envelopes which are serially numbered.

Blinding and masking

Parents of the newborns were blinded during the study. Analysis of the study was also blinded.

Protocol variations:

The following provisions were also made:

a. Interim analyses at the end of 6 months, to analyze the data to know any untoward effect.
b. For withdrawal of participants-

1. Parents withdraw consent

2. Life threatening complications: fulminant sepsis, shock – the baby may be withdrawn from the study.

For premature stopping of trial- If rapid nutrition was found to cause excessive mortality or life threatening complications the trial could be discontinued.

Data Safety Monitoring Board was established to intermittently review the progress of the trial.

Data Analyses:

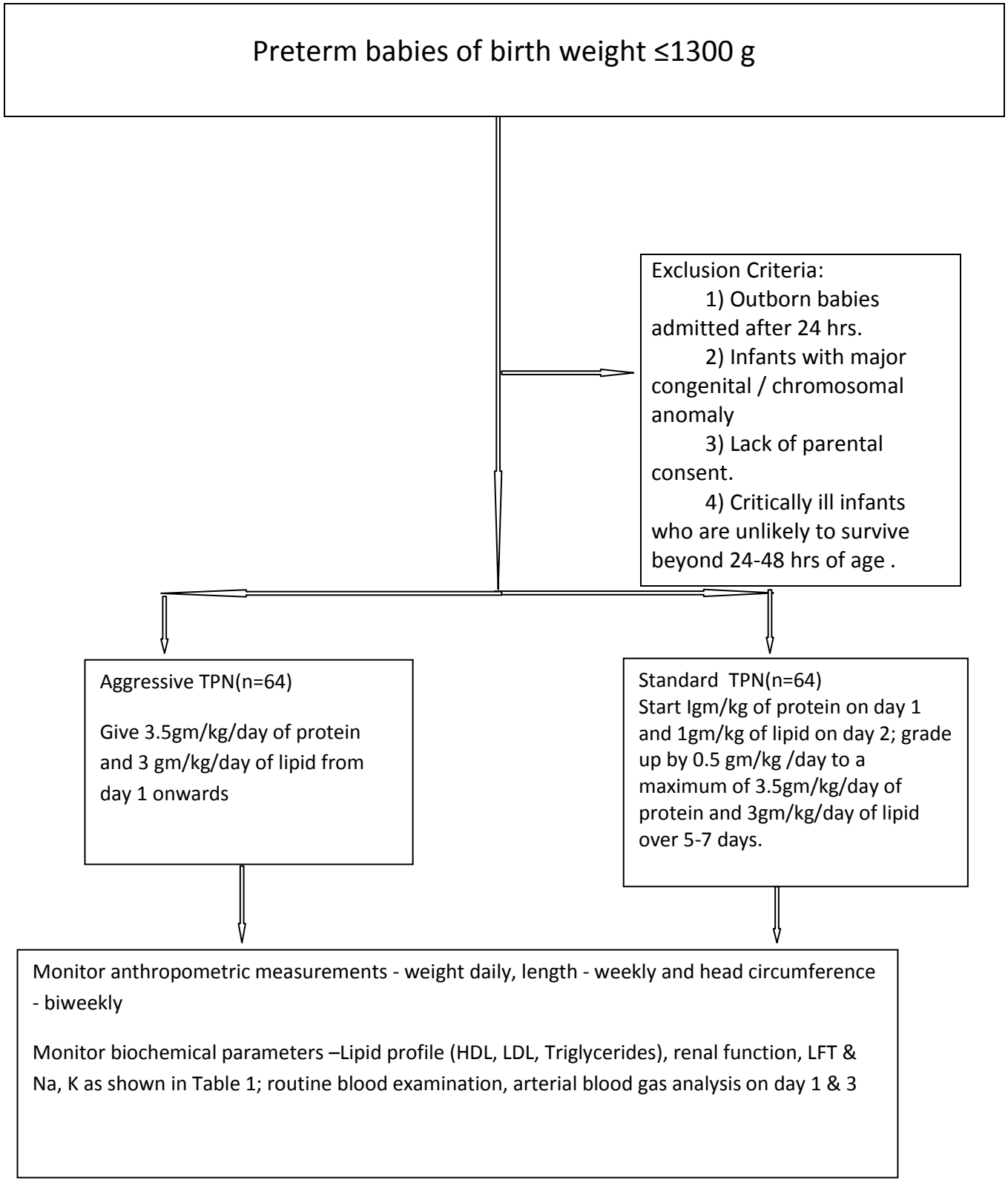
a. Statistical methods to be used for the primary outcome;

Primary outcome was assessed using independent t test or Mann Whitney U test.

b. Methods for additional analyses, if indicated.

The comparison between groups to regain birth weight was by log rank test. The number of days to discharge was compared by Mann Whitney U test. Morbidities between the groups were assessed by Chi-square test.

FIGURE 1


Preterm babies of birth weight ≤1300 g
Exclusion Criteria:
1) Outborn babies admitted after 24 hrs.
2) Infants with major congenital / chromosomal anomaly
3) Lack of parental consent.
4) Critically ill infants who are unlikely to survive beyond 24-48 hrs of age .
Aggressive TPN(n=64)
Give 3.5gm/kg/day of protein and 3 gm/kg/day of lipid from day 1 onwards
Standard TPN(n=64)
Start Igm/kg of protein on day 1 and 1gm/kg of lipid on day 2; grade up by 0.5 gm/kg /day to a maximum of 3.5gm/kg/day of protein and 3gm/kg/day of lipid over 5-7 days.
Monitor anthropometric measurements - weight daily, length - weekly and head circumference - biweekly
Monitor biochemical parameters –Lipid profile (HDL, LDL, Triglycerides), renal function, LFT & Na, K as shown in Table 1; routine blood examination, arterial blood gas analysis on day 1 & 3

RESULTS

During the study period extending from June 2013 to February 2014, 74 babies satisfying the inclusion criteria were recruited in the study. They were randomised into two groups of 37 babies in each arm. Schematic diagram for the results is shown below in Figure 2.

FIGURE 2.

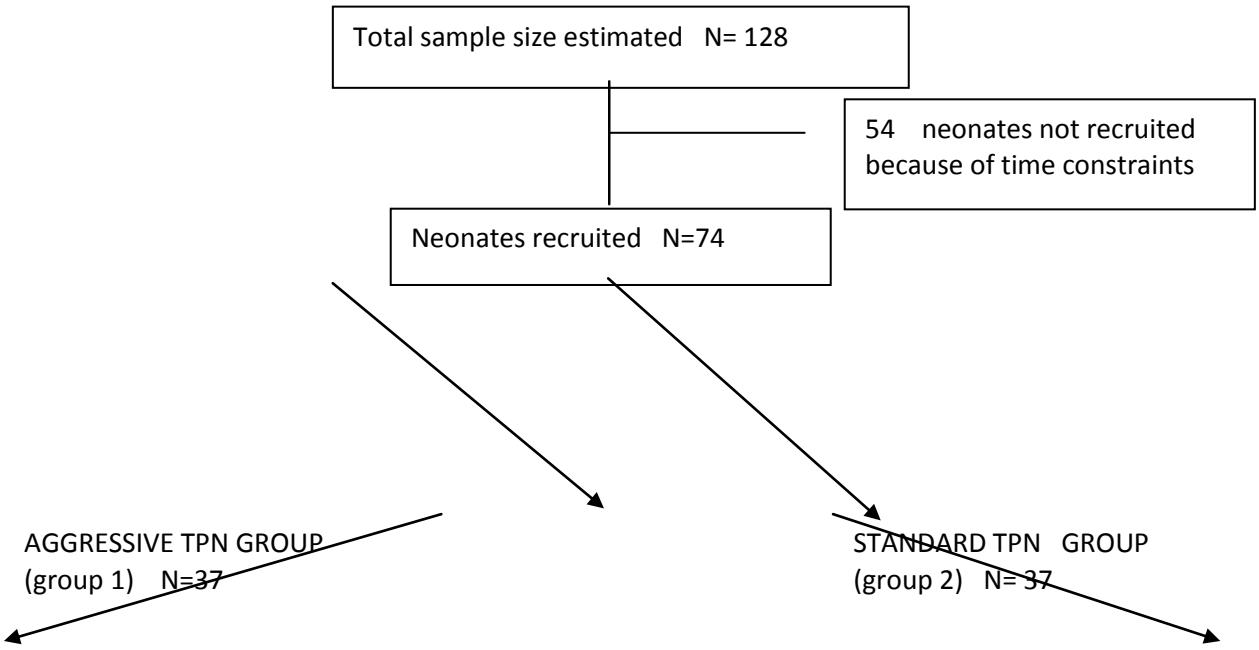


Table 3

DEMOGRAPHIC VARIABLES- MOTHER

VARIABLES	FREQUENCY	PERCENTAGE
Hypertension (PIH)	33	45.2
Diabetes	9	12.3
UTI	0	0
Chorioamnionitis	1	1.4%
Risk of sepsis	17	23.6%
Normal delivery	33	45.2

(n=74)

Table 3 shows the number of mothers with maternal morbidities like hypertension, diabetes, chorioamnionitis, and those who had normal vaginal delivery. 45.2% of mothers had hypertension (PIH), and 23.6% had risk factors for early neonatal sepsis. A majority of mothers delivered by LSCS (54.8%).

Table 4

DEMOGRAPHIC VARIABLES – MOTHER -AGGRESSIVE (GROUP 1) vs STANDARD (GROUP 2)

Variable	Aggressive TPN		Standard TPN		p
	Freq	%	Freq	%	
PIH	15	41.7	18	48.6	0.549
Diabetes	4	11.1	5	13.5	1.000
UTI	0	0	0	0	
Chorioamnionitis	0	0	1	2.7	1.000
Risk of sepsis	7	20	10	27	0.483
Normal delivery	33	45.2	40	54.8	0.20

Table 4 shows the frequency of maternal morbidities in the two groups. There was no significant difference in maternal morbidities such as PIH, DM, UTI, chorioamnionitis, risk of sepsis or mode of delivery between the two groups. 41.7% of mothers on aggressive nutrition and 48.6% of mothers on standard nutrition had a history of PIH; there was no significant difference between the groups.

The maternal characteristics were comparable in the two groups.

Table 5

DEMOGRAPHIC VARIABLES - NEONATE (AGGRESSIVE VS STANDARD)

	Aggressive TPN	Standard TPN	p
Gestational Age in (weeks) (Mean±SD)	30.2±2.2	30.7±2.59	0.42
<28 weeks	6	4	
28-32 weeks	24	24	
>32 weeks	7	9	
Birth Weight (g) (Mean±SD)	1080.9±136.8	1134±129.8	0.92
<1000g	10	6	
1000-1200g	20	20	
1200-1300g	8	13	
Head Circumference at birth (cm) (Mean±SD)	26.1±2.8	27.5±4.6	0.13
Length at birth (cm) (Mean±SD)	36.6±2.3	37.6±3.0	0.39

Table 5 shows the baseline demographic characteristics of the babies in the aggressive and standard groups in terms of gestational age, birth weight, length and head circumference.

The group of babies in the aggressive group were slightly more preterm compared to the standard group; however the difference was not statistically significant. Similarly, mean birth

weight was lower in the aggressive group compared with the standard, but it was not statistically significant (1080.9g vs 1134g, p =0.92).

The head circumference and length at birth was lower in the aggressive arm but the differences were not statistically significant.

ADMINISTRATION OF TPN

TPN was started within 24 hours of life in the recruited babies and was administered till babies tolerated 100ml/kg/day of nasogastric feeds, as per the study protocol. The average duration of TPN administration in days was compared between the two groups (mean 7.86±5.67 in aggressive group vs 7.57± 3.33 in standard group, p= 0.752) and the difference was not statistically significant.

FIGURE 3

COMPARISON OF MEAN WEIGHT BETWEEN THE TWO GROUPS

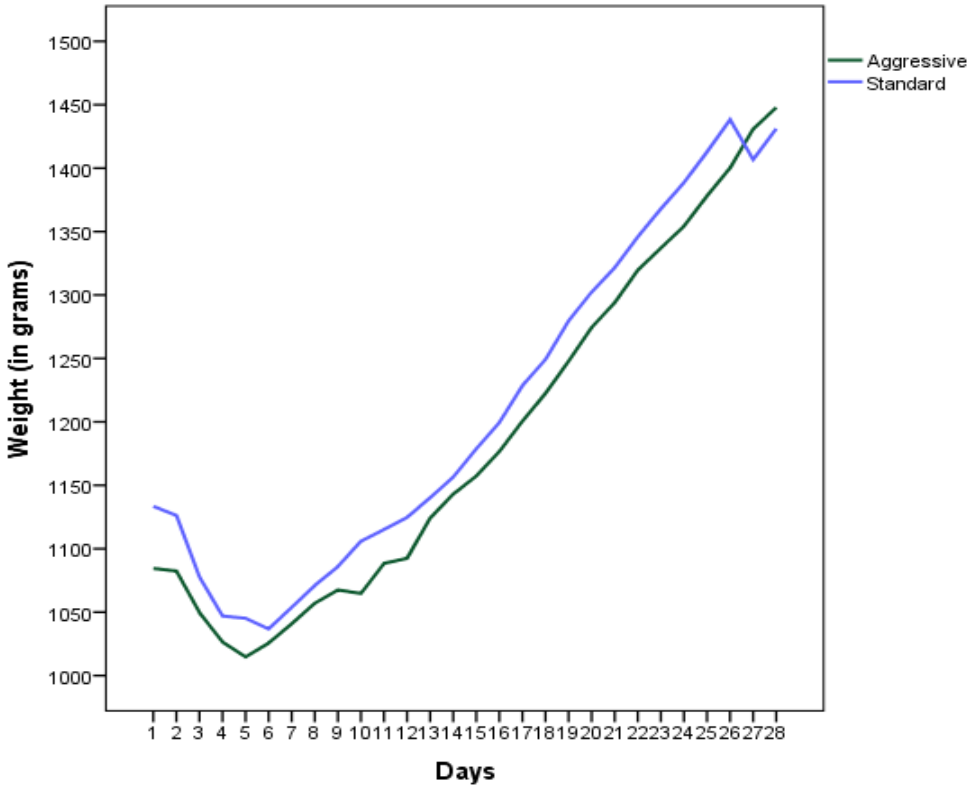


Fig 3 shows the difference in mean weight (in g) over 28 days after birth in both the study groups. As noted in Table 5, the initial mean birth weight in the standard TPN group was 54 g more than the aggressive TPN group. The difference slowly decreased during the study period. By 28 days, the mean weight in the aggressive group was higher than that in the standard group. However, the rate of weight gain was not significantly different between the groups.

FIGURE 4

COMPARISON OF THE MEAN LENGTH DIFFERENCE BETWEEN THE TWO GROUPS

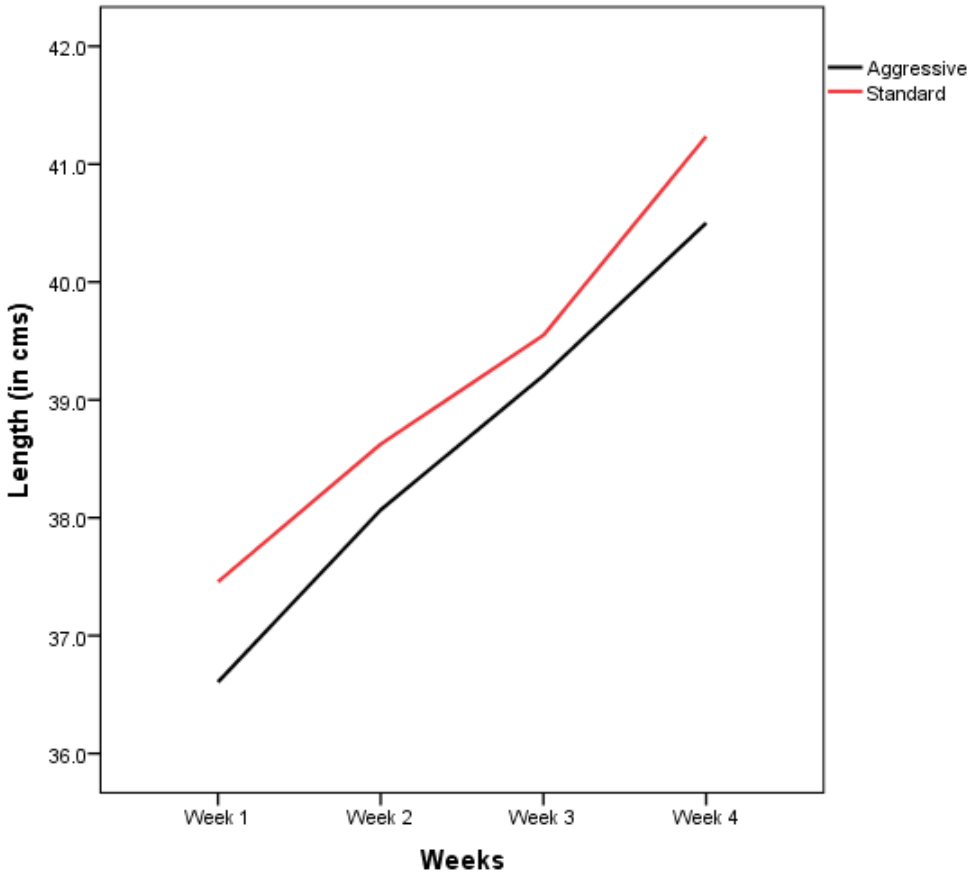


Fig 4 shows the comparison of mean length between the two groups. It can be seen that the initial difference in mean length is about 1 cm more in the standard group. However, the difference between the two groups decreases over 28 days, but the differences in the rate of growth were not statistically significant.

FIGURE 5

COMPARISON OF MEAN HEAD CIRCUMFERENCE BETWEEN THE TWO GROUPS

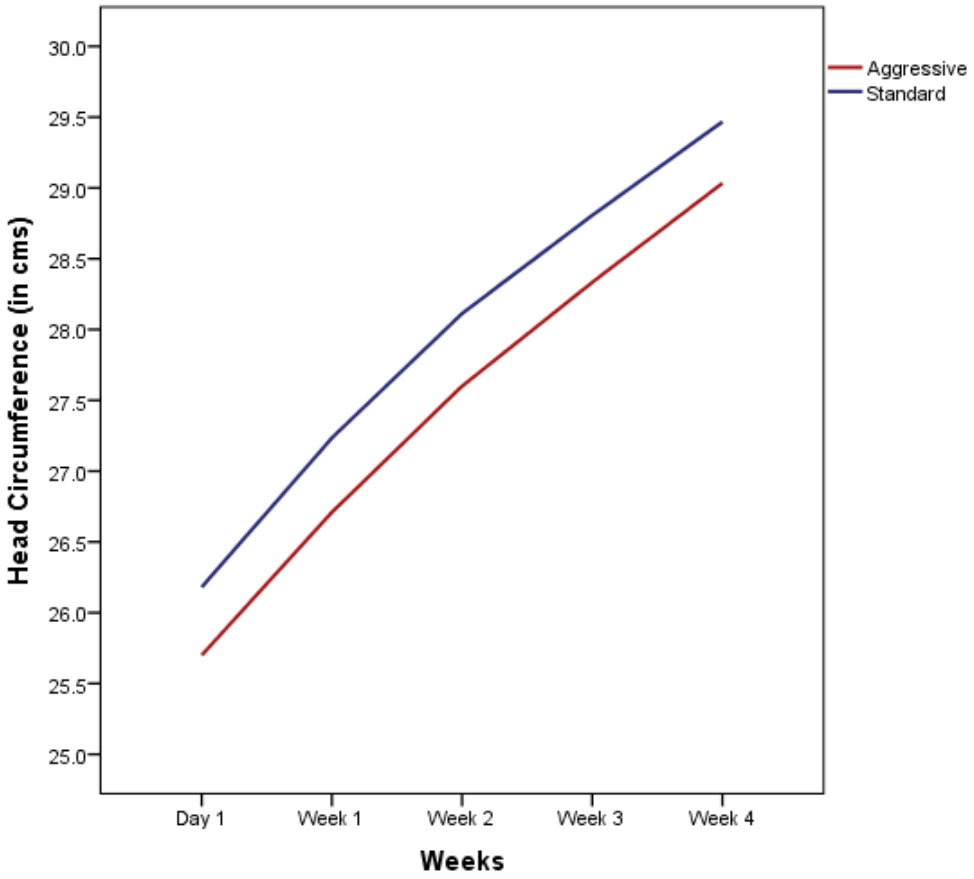


Fig 5 shows the mean head circumference in the two groups. It is seen that there is a difference in head circumference, higher in the standard group initially. There is a marginal increment in the head circumference in the aggressive group over a period of one month.

Table 6

CLINICAL VARIABLES IN NEONATES

VARIABLE	FREQUENCY	PERCENTAGE
Respiratory		
HMD	33	45.2
CPAP	37	50.7
Conventional Ventilation	16	21.9
HFOV	1	1.4
Surfactant administration	6	8.5
Central nervous system		
IVH	18	24.7
PVL	9	12.9
Cardiovascular system		
PDA	23	31.9
Ophthalmology		
ROP	7	10.6
Gastrointestinal system		
Feed Intolerance	15	21.1
NEC	4	5.6
Sepsis		
EOS	2	2.8
LOS	7	10.3
Probable sepsis	7	11.1
Mortality	7	9.5
DAMA	6	8

(Abbreviations: HMD-Hyaline membrane disease; CPAP- Continuous positive airway pressure; HFOV-High frequency oscillatory ventilation; IVH-Intraventricular hemorrhage; PVL-Periventricular leukomalacia; PDA-Patent ductus arteriosus; ROP-Retinopathy of prematurity;

NEC-Necrotising enterocolitis; EOS-Early onset sepsis; LOS-Late onset sepsis; DAMA-Discharged against medical advice.)

The various common morbidities of prematurity were analysed.

Hyaline membrane disease was seen in 45.2% of the babies. 37 babies (50.7%) needed CPAP for various respiratory disorders. 16 babies were ventilated (21.9%) and 6 babies received surfactant (8.5%). Only 1 baby needed HFOV.

23 babies(31.9%) developed PDA making it the second most common morbidity. 15 babies had feed intolerance (21.1%); 4 babies (5.6%) developed features of NEC.

18 babies developed intraventricular hemorrhage (24.7%): IVH grade 1/ 2 was seen in 14 babies and grade 3/4 was seen in 4 babies; PVL was noted in 9 babies (12.9%).

9 babies developed sepsis; 2 were early onset sepsis and 7 (10.3%) were late onset sepsis.

Table 7
CLINICAL VARIABLES IN NEONATES - AGGRESSSIVE VS STANDARD TPN

VARIABLE	Aggressive TPN		Standard TPN		p
	Freq	%	Freq	%	
Respiratory					
HMD	17	47.2	16	43.2	0.73
CPAP	19	52.8	18	48.6	0.72
Conv vent	7	19.4	9	24.3	0.61
HFOV	0	0	1	2.7	1.00
Surfactant	2	5.9	4	10.8	0.67
Central nervous system					
IVH	9	25	9	24.3	0.94
PVL	6	17.6	3	8.3	0.30
Cardiovascular	14	38.9	9	25	0.20
PDA					
Ophthalmology					
ROP	3	9.7	4	11.4	1.00
GI system					
Feed Intolerance	7	19.4	8	22.9	0.72
NEC	2	5.6	2	5.7	1.00
Sepsis					
EOS	1	2.8	1	2.9	1.00
LOS	4	11.8	3	8.8	1.00
Prob. sepsis	6	18.8	1	3.2	0.10
Mortality	4	10.8	3	8.1	0.64
DAMA	4	10.8	2	5.4	0.64

The various neonatal morbidities were analysed for differences in the two groups (Table 7). The incidences of HMD was quite high in both the groups but were comparable. The use of CPAP in both the groups was similar, also the use of conventional ventilation and surfactant.

The incidence of IVH was similar in both the groups: There appeared to be a higher incidence of PVL in the aggressive group (17.6% vs 8.3%) when the follow-up neurosonogram was done at 6 weeks of life, but it was not a statistically significant difference (p=0.30).

Similarly, the incidence of PDA was higher in the aggressive group but the difference was not statistically significant (38.9% vs 25%, p= 0.20). All babies with PDA were treated with indomethacin.

The differences in the incidence of ROP, NEC and feed intolerance between the groups was not significant. The incidence of definite sepsis was the same in both groups. However there was a higher incidence of probable sepsis in the aggressive group compared to the standard group, but the difference was not statistically significant (18.8% vs 3.2%, p= 0.10).

Table 8

OUTCOME VARIABLES IN NEONATES - LAB PARAMETERS (HAEMATOLOGICAL)

VARIABLES	Aggressive TPN		Standard TPN		p
	Freq	%	Freq	%	
Anaemia (Hb<14g/dL)					
Day 3	4	10	3	8	0.72
Day 7	14	37	11	29	0.64
Leucopenia (<5000cells/mm3)					
Day 3	5	13	8	21	0.65
Day 7	4	10	2	5	0.45
Thrombocytopenia (<150000/mm3)					
Day3	10	27	10	27	0.95
Day 7	12	32	10	27	0.80

The various haematological parameters that could be influenced by the study intervention were analysed in both groups. The babies were compared for the differences in blood counts - anemia, leucopenia and thrombocytopenia on two separate days. The two groups were similar.

Table 9
LAB PARAMETERS (ELECTROLYTES AND RENAL FUNCTION)

VARIABLES	Aggressive TPN		Standard TPN		p
	Freq	%	Freq	%	
Hyponatremia (<130meq/l)					
Day 3	32	88.9	35	94.6	0.43
Day7	23	67.6	22	73.3	0.61
Day 14	21	75	21	80.8	0.61
Day 28	27	93.1	25	92.6	1.00
Hypernatremia (>145meq/l)	2	5	6	16	0.56
Day 3					
Day 7	-	-	-	-	
Day 14	1	2	2	4	0.49
Day 28	1	3	-	-	
Hypokalemia(<3.5meq/l)Day3	6	16.7	6	16.2	0.95
Day 7	7	20	3	9.7	0.20
Day 14	7	23.3	3	11.1	0.44
Day 28	4	13.1	0	0	0.11
Hyperkalemia(>6meq/l)Day3	6	16.7	3	8.1	0.30
Day 7	6	17.1	3	9.7	0.48
Day 14	1	3.3	3	11.1	0.33
Day 28	1	3.3	3	10.7	0.34
Raised Blood Urea >32mg%					
(N 2.1-32 mg%) Day3	8	21.6	7	18	0.54
Day 7	20	69	14	46.7	0.83
Day 14	9	33.3	5	25	0.53
Day 28	2	8	3	12.5	0.66
Hypercreatininemia					
(N 0.8-1.6mg/dL) Day3	19	52.8	23	67.6	0.20
Day 7	26	78.8	27	90	
Day 14	23	82.1	24	100	0.54
Day 28	28	96.6	26	100	1.00

N = normal range

The effect of the intervention on electrolyte levels was also assessed. There was no significant difference in the sodium and potassium levels in both groups when analyzed on four separate occasions.

The effect of the higher amounts of protein on urea levels was also assessed four times in the study period; there was no significant difference between the groups although a higher percentage of babies with aggressive TPN had elevated blood urea levels.

Table 10

LAB PARAMETERS (LIVER FUNCTION, LIPID PROFILE)

VARIABLES	Aggressive TPN Freq	%	Standard TPN Freq	%	p
Direct bilirubin(N =2 mg/dL) *Day 7*	1	3.6	1	4	1.00
Day 28	0	0	1	3.8	1.00
Increased ALP (N 107-474IU/L) *Day7*	4	14.3	3	11.5	1.00
Day 28	11	45.8	12	46.2	0.98
Increased AST(N 16-67 IU/L) *Day 7*	5	17.9	5	19.2	0.52
Day 28	7	30.4	8	30.8	0.98
Increased ALT(N 10-40 IU/L) *Day 7*	5	17.9	0	0	0.52
Day 28	0	0	2	7.7	0.49
Hypertriglyceredemia(N 34-208 mg/dl)*Day 7*	6	20.7	7	26.9	0.58
Day 28	3	13	3	11.5	1.00
Hypercholesteremia(N 56-156 mg/dl)*Day 7*	6	20.7	4	15.4	0.45
Day 28	2	8.7	1	3.8	0.59

N = normal range

The effect of TPN on liver function tests and the possibility of cholestasis was also studied. There was no difference in the direct bilirubin levels (3.6 vs 4%, p=1.00) and alkaline phosphatase levels (14.3% vs 11.5%, p= 1.00) between the aggressive and standard groups.

The incidence of hypertriglyceridemia was assessed on day 7 (20.7% vs 26.9%, p=0.58) and day 28. On day 28 of life, when the estimation was done, none of the babies were on TPN. However, on both days, the differences in levels between the aggressive vs standard group was not statistically significant.

The frequency of higher levels in case of serum cholesterol, creatinine and liver enzymes were comparable between the groups.

Table 11

LAB PARAMETERS (BLOOD GAS)

VARIABLES	Aggressive TPN		Standard TPN		P
	Freq	%	Freq	%	
PH <7.32 (N 7.32-7.40)	13	35	14	37	0.95
$paCO_2$>36 mmHg (N 33-36)	22	59	20	54	0.90
Metabolic acidosis (HCO3 <20 mEq/L	19	52.8	15	42.9	0.40
Base excess (>-5)	20	55.6	20	57.1	0.89

N = normal range

Lower values of serum bicarbonate levels were seen in a higher percentage in the aggressive group compared to the standard group (52.8% vs 42.9%, p= 0.40) but the difference was not statistically significant. Similarly, there was no significant difference between the groups regarding $paCO_2$ levels on day 3 of life (59% vs 54%, p= 0.90).

Table 12
PRIMARY OUTCOME VARIABLES (NEONATE)

	Aggressive TPN	Standard TPN	p
Weight gain (gm/kg/day)	10.06±4.11 SD	9.61±3.91 SD	0.66
Increase in length (cm/week)	1.11±0.55 SD	0.98±0.62 SD	0.40
Increase in head circumference (cm/week)	0.80±0.19 SD	0.79±0.23 SD	0.82

Table 12 shows the effect of the two methods of TPN administration on the primary outcome variables viz. rate of weight gain, length, and head circumference.

The babies in the aggressive group gained more weight when compared to the standard group but this difference in rate of growth was not statistically significant (mean 10.06 vs 9.61 , p=0.66).

The gain in length in cm/week was also higher in the aggressive group, but it was not significantly different (mean of 1.11 vs 0.98,p= 0.40).

The increase in head circumference in cm/week was more in the aggressive group (0.80 vs 0.79, p=0.82) but the results were not statistically significant.

Table 13

SECONDARY OUTCOME VARIABLES

	Aggressive TPN	Standard TPN	p
Time to regain birth weight (days) (Mean +/-SD)	12.53±4.31	14±5.62	0.261
Time to reach full NG feeds (days) (Mean +/-SD)	11.73±4.60	10.79±3.86	0.609
Duration of TPN (days)(Mean +/-SD)	7.86±5.67	7.57±3.33	0.752

The time to regain birth weight was more in the standard group compared to the aggressive group, but the difference was not statistically significant.

The time to reach nasogastric feeds of 100ml/kg/day was longer in the aggressive group, but not significantly different (mean 11.73 days vs 10.79, p= 0.60).

The number of days the babies were on TPN in both groups was also comparable (mean 7.86 days vs 7.57, p=0.752).

DISCUSSION

Preterm infants need calories in the range of 80-120 Kcal/kg body weight in the first few weeks of life (1). Early adequate nutrition in preterm babies is essential to improve their neurodevelopmental outcome (2). However these infants may not be able to absorb the vital components of milk like their term counterparts because of immaturity of the gut. Hence, they are frequently on TPN in the first few days of life. The most appropriate mix of amino acids, carbohydrates and lipids to be provided as TPN has not been determined. Also, there is lack of consensus on the timing, dose and indications for preterm TPN administration.

This study aimed to compare two different regimens of protein and lipid administration, to examine the effect on growth of the preterm during hospital stay and to determine if there were excessive adverse effects due to TPN.

It is important for us to ascertain the ideal amount of lipid and amino acid that a baby needs for adequate growth. In many neonatal units including our unit, the standard practice has been to start TPN on day 2 and slowly grade up amino acids and lipids over a period of 5-7 days. Few studies have used higher amounts of lipid and amino acid from day 1 onwards (4).

In our study, infants with birth weight ≤1300g meeting the inclusion criteria were enrolled.

Babies were randomly allocated to receive either the standard TPN regimen or aggressive TPN. The aggressive TPN group was given 3.5g/kg of amino acid and 3 g/kg lipid each along with 10% dextrose (8-10 g/kg/day) within 24 hours of birth. Babies in the standard TPN group were started on 1g/kg of amino acid on day one and 1 g/kg/day of lipid on day 2, along with 10% dextrose (8-10 g/kg/day). Amino acids and lipids in this group were then increased by 0.5 g/kg/day till 3.5 g/kg/day of amino acids and 3 g/kg/day of lipids was achieved.

Babies in both groups were given TPN via an umbilical or percutaneous long line. TPN was continued until a limit of 100ml/kg of enteral feeds was reached. The tolerance to TPN was monitored using lab parameters and anthropometric measurements were compared between the groups. The time taken to reach full feeds and the time taken to regain birth weight was also compared.

Anthropometric measurements and comparison

At birth, babies in the standard TPN group were larger than the aggressive group in all three anthropometric measures viz. weight, length and head circumference. Mean birth weight was higher in the standard group by 67 gm compared to the aggressive group. The mean difference in length was more in the standard group by 45mm compared to the aggressive group. Similarly, the mean head circumference was more in the standard group by 0.5 cm compared to the aggressive group.

The rate of growth over the first 28 days of life showed that the aggressive TPN group babies grew faster in all parameters: weight in gm/kg/day (10.06±4.11 vs 9.61±3.91, p= 0.66), length in cm/week (1.11±0.55 vs 0.98±0.62, p=0.40) and head circumference in cm/week (0.80±0.19 vs 0.79±0.23, p=0.82). However these differences were not statistically significant. Valentine et al (34) 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). Analyses at 36 weeks CGA indicated fewer infants below 10^{th} centile in early amino acid group (23.7%) vs late amino acid group (41.7%) (p <0.0001; 95% CI-27.6 to -8.30) as interpreted by the Fenton chart. Our study also did not show any significant difference in mean weight gain between the groups, despite administering lipid in addition to amino acids.

Tan et al (17) noted that the relationship between head growth and cumulative energy intake was statistically significant (correlation coefficient R=0.44). Similarly, the relationship between head growth and cumulative protein intake was also statistically significant (correlation coefficient R=0.34). However, there was no statistically significant difference between the groups at 36 weeks gestation in terms of weekly increments in the first 7 weeks of life regarding OFC, length and weight. This was similar to our study which also did not show significant difference in the first 4 weeks of life.

Wilson et al (66) noted that there was no significant difference in median duration of time to discharge or death between the aggressive and standard regimens based on his criteria. Early growth in the initial period of hospital stay, and late growth in the last week before discharge from the hospital was better in the aggressive group. Wilson et al also noted that the maximal percent of weight loss from the birth weight was significantly lower in the aggressive group when compared to the standard group (5.1% vs 8.4%, $p < 0.05$). This was different from our study which did not show any such difference. Wilson et al (66) also noted that the weight $<10^{th}$ centile at discharge was lesser in the aggressive group compared to the standard group (59% vs 82%, $p < 0.05$) the difference being statistically significant. However the change in length (56% vs 74%) and head circumference (14% vs 30%) showed a trend favouring the aggressive group, but it was not statistically significant.

Porcelli et al (28) noticed that there was a mild increase in the mean weight gain of babies on higher amino acid (4g vs 3g) and noticed that there was more weight change from birth in the higher amino acid group (46.4; CI 14.6-78.2) vs the lower amino acid group (36.1; CI 7.5-64.8) but this was not statistically significant. Our study did not show any change even after the addition of lipid with amino acid.

Ibrahim et al (64) showed that slow grading up of lipid was unnecessary. He also noted that higher intralipid administration fulfilled EFA deficiency with no effect on plasma triglyceride and cholesterol.

Adequate Enteral Nutrition

The number of days to reach full feeds was compared in our study between the aggressive and standard group (11.73±4.60 vs 10.79±3.86, p=0.60) and there was no significant difference. Tan et al (17) demonstrated that it took around 19 days to reach full enteral feeds in the intervention group compared to 15 in the control group. Wilson et al (66) noted that the number of days to full feeds showed a median interquartile range of 13-30 days in aggressive group vs 16-30 days in slow group. Valentine et al (34) noted that infants in early amino acid group achieved full enteral nutrition earlier compared to the lesser amino acid group (8.3 days to 9.9 days, p <0.039). Porcelli (28) compared the time to attainment of full feeds between the two groups and it was noted to be similar. There was no significant difference in these studies between the intervention and control groups regarding the time to attain full feeds, similar to the present study.

Regaining Birth Weight

In the study by Tan et al (17), 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). Wilson et al (66) found that the time to regain birth weight was 6-11 days (IQR) in the aggressive group vs 9-17 days in standard group (p<0.001).

In our study, the number of days to regain birth weight was less in the aggressive group vs standard group (12.53±4.31 vs 14±5.62, p= 0.261) but difference did not reach statistical significance.

Comparison of morbidity

Clinical parameters

The incidence of various morbidities that occurred in preterm babies was compared. The results were similar to other studies in not showing any significant difference in the common morbidities of prematurity.

The incidence of severe intraventricular hemorrhage (IVH) or parenchymal damage was not significantly different between the two groups. Similarly the incidence of other common morbidities of prematurity like hyaline membrane disease (HMD), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), necrotising enterocolitis (NEC) and sepsis were compared between babies in the aggressive and standard TPN groups; it did not show any significant difference between the arms.

Tan et al (17) noted that 6 babies in the intervention group (n=55) and 8 (n=59) in the standard group developed severe IVH; however the results were not statistically significant. Similarly, 6 babies each in both groups developed NEC.

Valentine et al (34) compared early amino acid administration to late amino acid in preterm infants and noted that the incidence of IVH (24.2% vs 21.1%,p=0.475), NEC (5.30 vs 7.14%, p=0.451), PDA (27.7% vs 32.4%, p=0.27) and BPD (18.9% vs 27.2%, p=0.05) did not show any statistically significant difference.

Porcelli et al (28) compared the limits of tolerance of the baby to 4g and 3g of amino acid and came to the conclusion that there was no significant difference in the incidence of IVH (6 in each group) or ROP (2 in each group). However there was a significant difference in the incidence of BPD between the two groups (higher in lower amino acid group 14, vs high 2, p <0.006). Because our study period was till 28 days of life, we did not evaluate the incidence of BPD in our study.

Ibrahim et al (64) compared common morbidities of prematurity like BPD, IVH, PDA, ROP (BPD 8 vs 9 in aggressive vs standard group 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 between the two groups.

Wilson et al (66) compared fast vs slow grading of amino acid and lipid and could not demonstrate any statistically significant difference in the incidence of NEC (8% vs 7%), HMD (61% vs 56%), BPD (22% vs 23%) or osteopenia of prematurity (9% vs 5%).

We assessed these parameters between the groups: IVH (17.6% vs 8.3%, p= 0.30), PDA (38.9% vs 25%, p= 0.20), ROP (9.7vs 11.4%, p= 1.00), NEC (5.6 vs 5.7%, p= 1.00), PVL (17.6 vs 8.3%, p= 0.30) and HMD (47.2 vs 43.2%, p= 0.73). Similar to other studies, there was no statistically significant difference between the two groups. Since many of our babies were of a higher gestational age and the average length of stay was less than 4 weeks, BPD was not assessed as a secondary outcome measure.

Laboratory parameters

Haematological*:* The effect of the doses of TPN on haematological parameters was assessed. There was no difference in the incidence of anaemia (10 vs 8%, p= 0.72), leucopenia (13 vs 21%, p= 0.65) and thrombocytopenia (32 vs 27, p=0.80) between the aggressive and standard TPN groups.

Blood Urea*:* The factor of raised urea secondary to the high administration of amino acid has been studied. Studies have shown varied results on the effect of the dose of amino acid on blood urea nitrogen. Certain studies have documented higher urea levels secondary to higher amounts of TPN. Thureen et al (71) could not see any significant effect on blood urea levels with change in amino acid intake (r^2=0.08). Blanco et al (65) noted that blood urea levels were significantly high on day 1 and 7 along with the urine BUN in the early high intervention group

compared with the standard group (p<0.01). Porcelli et al (28) compared the tolerance levels of 4g of amino acid to 3 g of amino acid and came to the conclusion that there was mild increase in BUN in the second week of life. However, there was no statistically significant difference in blood urea between the groups in our study (21.6% vs 18% on day 3, p =0.54) with the normal levels of urea taken as 2.1-32 mg/dL; the babies in the aggressive group tolerated the higher amount of protein similar to the standard group.

***Liver Function**:* Since there is concern about the effect of TPN on liver function and development of cholestasis, LFTs are done as a part of evaluation during TPN administration. In our study, we used predefined criteria for cholestasis and compared the two groups. Comparison was done for high direct bilirubin on day 7 (3.6% vs 4%, p= 1.00), high alkaline phosphatase (14.3% vs 11.5%, p =1.00) and raised liver enzymes (high AST 17.9 vs 19.2%, p=0.52); there was no difference between the groups in our study.

Colomb et al (60) studied the effect of cholestasis secondary to TPN administration and noted that 10 children on TPN had a total of 24 episodes. 17 of the episodes normalised after discontinuation of lipids for a brief period. Amin et al (38) has studied the effect of rise of free bilirubin secondary to lipid administration and noticed that at gestational age <28 weeks, bilirubin levels increased significantly for lipid administration above 1.5g/kg/day. Wilson et al (66) compared fast vs slow grading of amino acid and lipid and there was no statistically significant difference between the groups in terms of hyperbilirubinemia (41% vs 38%). In the study by Tan et al (17) the incidence of cholestasis was 16 in the intervention group (n=55) and 13 in the control group (n=59), with no significant difference. Ibrahim et al (64) also did not notice any difference in the value of mean bilirubin levels in the intervention arm when compared to control arm. The only significant adverse event was that peak serum bilirubin values were greater in early TPN compared to late TPN group (7.7 vs 6.1 mg/dl, p<0.002).

***Triglycerides**:* The relationship between aggressive lipid administration and hypertriglyceridemia and hypercholesteremia was not significant in our study. Murdoch et al (67) compared serum triglyceride concentrations before and after feeds and could not identify any statistically significant difference (0.2 vs 0.29 SE). Wilson et al (66) noted that there was no statistically significant higher incidence of triglyceridemia (43% vs 33%,p >0.01)or hypercholesteremia (55%vs33%, p >0.01). Thureen et al (71) also noted that there was no significant difference (0.69 ± 0.16mg/dl vs 0.72± 0.14mg/dl) between them. Ibrahim et al(64) also found no significant differences in the levels of triglyceride and cholesterol between the two arms. In our study there was no significant difference in the triglyceride levels (20.7 vs 26.9%, p= 0.58 on day 7) or cholesterol levels (20.7 vs 15.4%, p =0.45). The triglyceride levels were estimated on day 7 of life with the mean duration of TPN administration being around 7-8 days (mean 7.86±5.67 vs 7.57±3.33 in both arms, p =0.752).

***Dyselectrolytemia**:* The incidence of dyselectrolytemia was compared between the two groups. Blanco et al (65) studied the effect of high amino acid on metabolic parameters and noted that hyperkalemia or other factors were not of significant value. Similarly, in our study, there was no difference in the incidence of hyperkalemia (16.7 vs 8.1, p= 0.3 on day 3), hypokalemia (16.7 vs 16.2, p= 0.95 on day 3), hypernatremia (5 vs 16%, p= 0.56) and hyponatremia (88.9 vs 94.6, p= 0.43 on day 3) in relation to the intervention. The majority of cases had hyponatremia on day 3 between 125-130 mEq/L.

There was a high incidence of metabolic acidosis in both the groups on day 3 of life (serum bicarbonate levels <20 mEq/l) (52.8% vs 42.9%, p= 0.40). Probably the acidosis may be related to the morbidities involved and not due to the intervention. Blanco et al (65) noted that the serum bicarbonate level was higher in the early group along with higher intake of sodium acetate compared to the standard group (p <0.01). Porcelli et al (28) compared the tolerance levels of 4g of amino acid to 3 g of amino acid and came to the conclusion that higher amino

acid intake did not affect the mean serum bicarbonate level in the second week of life (23.9 ±2.9mEq/dl vs 19.1± 1.8 mEq/dL). Thureen et al (71) compared the base deficit (mean base deficit-3.4 ± 0.6 in the low group vs -4.1 ± 0.7 mEq/L in the high group) and there was no statistically significant difference between the groups. Base deficit measurement in our study also shows that a large proportion of babies had increased base deficit, but there was no difference between the aggressive and standard TPN groups (55.6% vs 57.1%, p= 0.89). Ibrahim et al (64) in his study also could not demonstrate any significant difference in the levels of serum bicarbonate in the intervention arm when compared to the control arm.

Effect on ventilation

The effect of lipid administration and the need for ventilation was compared. In our study, only a slightly higher percentage of babies in the standard group needed ventilatory support thus emphasising that early high doses of lipid or amino acid administration did not appear to affect oxygen requirement. CPAP was administered in a significant number of babies in both groups (52.8% vs 48.6%, p= 0.72), and conventional ventilation was required in a large number of cases in both the groups (19.4% vs 24.3%, p =0.61). pCO2 levels were high (>36mmHg) but similar in both groups (59 vs 54%, p =0.90).

The European guidelines recommend a maximum of 3-4g/kg/day of lipids in infants. Gilbertson (42) noted that when lipid infusion rate was not exceeding 0.15g/kg/hr, VLBW babies can tolerate lipids. In the study by Tan et al (17), the number of ventilator supported days were statistically significant in the intervention group (10 days vs 4, p<0.05). However, there was no statistically significant difference between the groups in terms of oxygen requirement at 36 weeks PMA (40 vs 36 preterms). Wilson et al (66) also found similar ventilatory requirements between the aggressive and standard nutrition groups (84% vs 77%). Porcelli (28) noted that the carbon dioxide production rate was significantly higher in the high

amino acid group (252 ± 8 micromol/kg/min EAA versus 224± 7 in LAA , p<0.01). Thureen et al (71) also found carbon dioxide production rate was higher in the high amino acid group.

Sepsis

In our study, the incidence of early onset sepsis (2.8 vs 2.9%, p= 1.00) and late onset sepsis (11.8 vs 8.8%, p= 1.00) was comparable between the groups. The organisms in our study were Klebsiella (4; 2 vs 2 in each group), NFGNB (2; 1 in each group), Acinetobacter (2 vs 0) and MRSA (1 in standard group). Freeman et al (62) 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). Tan et al (17) and Ibrahim et al (64) noted that there was no statistically significant difference between the two groups in term of sepsis (6 vs 7, p=0.73). Valentine et al (34) compared early to late amino acid administration in preterm infants and could not identify any significant difference in bacteremia between the groups (7.5% vs 11.4%, p=0.215). Wilson et al (66) also compared the incidence of bacteremia in the two groups and the odds ratio of bacterial or fungal bacteremia was 0.5 (CI 0.3-1.1); for coagulase negative staphylococcus bacteremia, it was 0.6 (CI 0.3-1.3).

Mortality

Mortality was compared between the two groups in various studies. Ibrahim et al (64) could not find any statistically significant difference in mortality between the groups, though sample size was low. Wilson et al (66) compared mortality and noticed that odds ratio was 0.9 (95%CI 0.4-2.1) which was not statistically significant. In the present study, 7 babies died during hospitalization (10.8 vs 8.1%, p =0.64); mortality was not statistically significant different between the groups.

Duration of TPN Administration*:* Our study compared the duration of TPN administration in both arms and the days of administration was noted to be similar (7.86±5.67 vs 7.57±3.33,

p=0.752). Tan et al (17) found that the intervention group needed a longer duration of TPN compared to the control arm (median of 17 days vs 12 days, $p<0.05$); the result was statistically significant. Wilson et al (66) also noted that the number of days for which lipid was administered had a median of 20 days (12-28 IQR) in the aggressive group vs 6 days (2-15 IQR) in the control group, $p<0.001$.

Our study noted that there was a small positive trend in the determinants of growth viz. weight, length and head circumference in the aggressive TPN group as compared to the standard group but the difference was not statistically significant.

The various common morbidities of prematurity such as HMD, PDA, IVH, NEC and ROP were analysed in both groups and there was no statistically significant difference between them. The secondary outcomes such as time to attain full nasogastric feeds and the number of days to regain birth weight were also comparable.

CONCLUSIONS

1.Higher doses of amino acid upto 3.5g/kg and lipid 3g/kg from day one shows a trend towards a positive difference in the determinants of growth (weight, length and head circumference) when compared to the standard grading of total parenteral nutrition in babies ≤1300g. However the difference was not statistically significant in this study.

2. Preterm babies could tolerate higher amounts of amino acid and lipid without any risk of adverse metabolic factors such as uremia, hypertriglyceredemia and cholestasis.

3. There was no significant difference in the incidence of common morbidities of prematurity like HMD, PDA, IVH, NEC, ROP or ventilatory requirement in the aggressive TPN group when compared to the standard group.

4. The number of days needed to attain full nasogastric feeds in the aggressive group was more compared to standard group but the difference was not statistically significant. Similarly, time taken to regain birth weight was less in the aggressive group compared to standard group, though the difference was not statistically significant in this study.

LIMITATIONS

1. In this study, babies received TPN for an average duration of 7-8 days which may not have been long enough to show a significant difference in growth.

2. The inclusion criteria to enrol babies in this study was those whose birth weight was below 1300g. Selection of more babies below 1000g (ELBW) could have yielded more precise data as TPN would normally be required for longer periods in them.

3. The required sample size could not be attained because of time constraints.

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ANNEXURE

INFORMATION SHEET

Study Title: *A randomized trial comparing aggressive vs slower grading up of total parenteral nutrition in very low birth weight preterm babies.*

You are requested to participate in a study that involves giving IV nutrition to preterm babies in the first few days of life. IV nutrition given as glucose (carbohydrate), protein and fat is referred to as total parenteral nutrition (TPN). Total parenteral nutrition administration to newborn babies is part of the standard care in the nursery. We plan to compare giving TPN in the usual way (slowly increasing the amount over 5-7 days) versus higher amounts of TPN from day 1.

What does high amounts of total parenteral nutrition do?

Total parenteral nutrition gives increased amounts of carbohydrates, protein and fat which will give high energy to the baby and probably facilitate faster growth. This may help in early recovery from illnesses and may make it possible to discharge early.

Does total parenteral nutrition have any side effects?

The practise of giving total parenteral nutrition is the standard treatment in very low birth weight babies. Rarely large amounts of lipid may cause increase in oxygen requirement and infection. Similarly large amounts proteins may interfere with the metabolism and cause accumulation of waste products. However, such complications are rare and so regularly monitoring babies in the nursery and doing blood tests can help in detecting any problems that might occur. If required, in babies who develop problems, giving TPN can be modified or omitted.

What will the process be if I give consent for the study?

If consent is given, your baby will be allocated to one of two groups - one in which there is full amount of TPN from day 1 and in the other group, there will be slow grading up of TPN. The grouping is done by a random process using sealed envelopes. The doctor nor the parents would have a say in deciding which of the patients will receive aggressive TPN and who will receive standard grading of TPN.

There will be regular checking of the lab tests to give an idea of the tolerance levels of the baby with regard to the type of nutrition. At the end of 28 days, babies in both groups will be checked for increase in weight, length and head circumference.

Can you withdraw from the study after it starts?

Your participation in the study is entirely voluntarily. You are also free to withdraw permission to participate in this study. If you do so, this will not have any bearing to the treatment given in the hospital. If any untoward incident is noted in any of the groups, the baby will be withdrawn from the study and appropriate treatment given.

What will happen if any study related injury happens?

As total parenteral nutrition is part of normal treatment for all preterm babies, we do not expect any major side effect or problem in both the groups. If at all any untoward problem happens, related to the total parenteral nutrition, we would treat the patient free of cost. We will be unable to provide any monetary compensation.

Will you have to pay for the study?

You will not need to pay for participating in the study. All blood tests done as part of the study will be done free of charge.

- What happens when the study is over?

The baby will be followed up in the outpatient regularly and growth parameters and development monitored. Later, we can compare the baby with the earlier values in the newborn period.

- Will your personal details be kept confidential?

The results of the study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further queries, please ask Dr Binu Govind 9787763448 or e mail to drbinugvnd@yahoo.com

CONSENT TO TAKE PART IN A CLINICAL TRIAL

Study Title: *A randomized trial comparing aggressive vs slower grading up of total parenteral nutrition in very low birth weight preterm babies.*

Study Number:

Participant's name:

Date of Birth / Age (in days):

I_____

_____, father/mother of _____

(Please tick boxes)

Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]

I also understand that the participation of my baby in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

I also understand that neither I, nor my doctors, will have any choice or knowledge of whether my baby will get aggressive or slow grading up of total parenteral nutrition.[ ]

I also understand that the practise of giving the different grades of total parenteral nutrition is part of the regular care and it will not cost anything more. [ ]

I understand that my baby will receive free treatment for any study related injury or adverse event but I will not receive and other financial compensation [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if my child withdraw from the trial. I agree to this access [ ]

I understand that the identity of my son/daughter will not be revealed in any information released to third parties or published [ ]

I voluntarily agree to take part in this study [ ]

Name:

Signature / Thumb impression:

Date:

Name of witness:

Relation to participant:

Date:

PROFORMA

Name

Hosp No

Mother Hospital No DOB

Address Tel

	week 1		Week 2	Week 3	Week 4
Weight	D1				
	D2				
	D3				
	D4				
	D5				
	D6				
	D7				
Length	`				
Head circumference	24hrs				

Blood PARAMETERS

	1	3	7	14	28
Routine blood examination	√		√		
Arterial blood gas		√			
Se. Electrolytes, Urea, Creatinine		√	√	√	√
Liver function test			√		√
Lipid Profile			√		√

Assessment of comorbidities

feed intolerance - yes no

nec - yes no

if yes, stage

Sepsis yes no

if yes,

probable definite

organism-

Respiratory distress yes no

need for ventilation yes no

if yes, reason

Neurosonogram findings

day 3

day 7

PDA yes no

Time to regain birth weight

Time to reach full enteral nutrition