Nutrition

Total parenteral nutrition for premature infants: practice aspects

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Minimizing extra uterine growth restriction is a major factor in improving developmental outcomes of premature infants. Total parenteral nutrition is a valuable tool to provide nutrition soon after birth as preterm infants take time to establish enteral intake. Optimal growth is essential for premature infants to assure overall development. TPN supplementation is not without side effects, but a cautious and multidisciplinary approach helps to minimize potential morbidities.

TPN | SCAMP | essential fatty acid deficiency | SMOF | CLABSI

Introduction

Total parenteral nutrition is an invaluable tool in providing early nutrition to premature infants when enteral nutrition is not feasible. As, preterm infants are at risk of post-natal growth delay, TPN aids in receiving nutrients to approximate *in utero* accretion. Studies have shown that minimizing time to return to birthweight decreases the incidence of extra uterine growth restriction and improves post-natal growth and neurodevelopmental outcomes [1, 2]. Parenteral nutrition can be provided via a peripheral or central route depending on anticipated length of parenteral nutrition and other considerations. TPN should be well balanced with macro and micronutrients, to provide adequate protein and non-protein energy which is important for optimal overall growth and helps to minimize metabolic derangements.

TPN Goal and indications

The main goal of TPN is to provide optimal nutrition which mimics *in utero* nutrient accretion during a period of high metabolic demands. Studies have shown that in comparison to term infants, most premature infants, especially ELBW, take longer time to regain birth weight and when they start to grow, and are not able to sustain the rate of intrauterine growth [1, 3, 4, 5]. Extra uterine growth restriction issues are potentially greater for the infants who have marked comorbidities of prematurity or who are small to begin with, intrauterine growth restriction (IUGR), being one example. An early and aggressive nutritional approach has been shown to decrease post-natal growth restriction by reducing the time to return to birthweight and improving long term outcomes [6, 7, 8, 9]. While providing amino acids and energy, TPN also provides other minerals (e.g. calcium, phosphorus, zinc, manganese, iodine and copper) and vitamins. Indications for TPN in premature infants are depicted below:

1. Immature bowel- VLBW and ELBW infants
2. Intestinal inflammation- necrotizing enterocolitis
3. GI failure- sepsis, short bowel syndrome, ileus
4. Intestinal obstruction- strictures, atresia, imperforate anus
5. Infants with cardiac diseases which may limit fluid intake

Fluid and Energy requirements

Early in gestation, the fetus contains a higher proportion of total body water (TBW) with more extracellular compartment water than intracellular. As gestation advances, extracellular water and TBW decreases in proportion to the intracellular compartment because of rapid cellular growth and accretion of fat and protein in last part of pregnancy. TBW contributes only 75% of body weight, and almost half of this volume is located in the intracellular compartment in the term infant [10]. Premature infants have higher TBW content compared with their term counterparts, with the majority of extracellular volume being distributed in the interstitium [11]. Contraction of extracellular compartment occurs after birth by fluid movement from interstitium into intravascular space. Clinically, this period is marked by significant diuresis. Fluid volume and parenteral nutrition should be prescribed while understanding the physiologic changes, as excess fluid administration can alter this delicate balance and also has been associated with high incidence of morbidities such as patent ductus arteriosus, and bronchopulmonary dysplasia [12]. In stable preterm infants, resting energy expenditure is approximately 50-60 kcal/kg per day [13] with additional calories are needed for growth. To maintain adequate growth, approximately 90-120 kcal/kg per day [parenteral] is needed for the preterm infant; however requirement can increase with additional comorbidities. The recommended fluid and energy intakes in premature infants during the first week of life, are depicted in Table I.

Table I. Estimated fluid and energy requirement[a]

Premature infants	First week of life (mL/kg of body weight)	Energy intake (average estimation-kcal/kg/day)
< 1500 g	80 to 140	90-120
>1500 g	60 to 130	90-120

a-Agostoni C, 2010 [23]

TPN calories should be balanced appropriately in terms of protein and non-protein energy. Overall carbohydrates should contribute approximately 50% of the total energy while protein and fat should provide 30% and 20% respectively. Provision of optimal non-protein calories results in accomplishing an anabolic state and adequate protein accretion.

TPN components

A well balanced total parenteral nutrition should provide optimal carbohydrate, protein, fat, macro and micronutrients including vitamins.

Abbreviations: TPN-total parenteral nutrition, ELBW-extremely low birth weight (<1000 g birth weight), VLBW-very low birth weight (<1500 g birth weight), TBW-total body water, CLABSI-central line associated blood stream infection, AA-amino acid, ESPGHAN-European society for Pediatric Gastroenterology, Hepatology and Nutrition, AAP-American academy of Pediatrics, CDC-Center for disease control, PUFA-polyunsaturated fatty acid, IUGR-intrauterine growth restriction

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Carbohydrate

Glucose is the principle source of energy available to infants immediately after the birth, helping to preserve endogenous carbohydrate stores and prevent hypoglycemia. It is exogenously provided to infants in the form of dextrose via continuous infusion to match endogenous glucose production rate which is typically 5 to 8 mg/kg/min [14]. One gram of dextrose provides 3.4 kcal. Carbohydrates in total parenteral nutrition should account for 60-75% of non-protein energy [15, 16]. Studies have shown that premature infants especially extremely low birth weight infants are at risk for hyperglycemia particularly in the 1st week of life for various reasons such as immature glucose homeostasis, sickness with increased catecholamine levels and small mass of insulin dependent tissues [17, 18]. However, hyperglycemia frequently results from parenteral glucose infusion rates exceed endogenous glucose production rates; therefore, frequent blood sugar values should be measured in order to prevent and/or treat hyperglycemia. Hyperglycemia is defined as blood plasma glucose above 180 mg/dL [19]. Hyperglycemia is associated with increased morbidity such as severe IVH (intraventricular hemorrhage), increases risk for bronchopulmonary dysplasia, prolonged hospital stay and mortality [20, 21]. There is a wide variation in clinical practice among NICUs for treatment of hyperglycemia. The common initial practice to treat hyperglycemia is to lower glucose infusion rate either by reducing dextrose concentration or reduce fluid rate thus lowering the GIR. Basal GIR (~4mg/kg/min) should be maintained as glucose is the readily available fuel for the brain. Early provision of well-balanced TPN with AA and fat in addition to dextrose might prevent episodes of hyperglycemia in VLBW and ELBW infants. Routine use of insulin to treat hyperglycemia should be discouraged, as it is associated with increased episodes of hypoglycemia and mortality [22]. Another treatment strategy to consider for hyperglycemia is lowering the dose of lipid infusion, as the glycerol it contains is the major gluconeogenic substrate [24]. In comparison, excess carbohydrate administration results in hyperglycemia and net lipogenesis with subsequent visceral fat deposition [25, 26].

Protein

Supplementation of AA (Amino acids) through parenteral nutrition soon after birth is a fairly common practice in neonatal ICUs. The most widely used AA solution in the United States are Trophamine® (Kendall-McGraw Laboratories, Irvine, CA, USA), Premasol® (Baxter Healthcare Corporation, Deerfield, IL, USA) and Aminosyn-PF® (Abbott Laboratories, North Chicago, IL, USA). The goal of early supplementation is to prevent negative nitrogen balance and promote growth [27]. Fetal accretion of protein in late second trimester (~29 weeks) is approximately 2g/kg, so an intake of 3 to 3.5 g/kg of amino acid is required after birth to maintain endogenous protein stores, and promote anabolism, while keeping up with obligatory losses. Studies have shown that amino acid intake of 3 to 3.5 g/kg per day in first days of life is both safe and effective in promoting protein accretion [27, 28, 29]. While data for optimal composition of AA solution for TPN is conflicting [30], most commercial solutions have been designed to result in plasma amino acid profile similar to cord blood or that of a breast-milk fed term infant. There are practical challenges in optimal AA delivery such as solubility of specific AA [e.g., tyrosine and cysteine]. Cysteine must be added to TPN solution while compounding as it has been shown to improve nitrogen retention in premature infants [31, 32]. It also improves the solubility of calcium and phosphorus in TPN solution and also improves the retention of glutathione, an important antioxidant [33]. Glutamine, which is abundant in breast milk, is not included in any commercially available AA solution because of solubility issues. A multicenter randomized trial however found glutamine supplementation did not reduce mortality or decrease the incidence of late-onset sepsis in ELBW infants [34]. Stephens et [44] al studied 156 extremely low birthweight infants and found that higher first-week protein (up to 3.5 g/kg per day) and energy intakes are associated with higher Mental Development Index Scores at 18 months of age. While data on impact of high protein supplementation (3.5 g/kg per day) on long term neurocognitive outcomes are sparse, studies have shown clear benefit in terms of better growth at NICU discharge and head growth at 18 months [1, 38, 39, 40]. High amino acid supplementation is both safe, effective and not associated with hyperammonemia, uremia or metabolic acidosis [41, 42]. A recent study by Morgan et al [43] showed that providing standardized concentrations and added macronutrient parenteral solution (SCAMP: ~30% more protein, lipid and carbohydrate) results in improved head growth in VLBW infants as compared to standardized parenteral solution [43]. Other studies have shown improved head growth results in improved neurodevelopmental outcomes [44, 45].

Currently there is no reliable marker for protein accretion, utilization and tolerance for premature infants besides weight gain. Use of serum BUN (blood urea nitrogen) as a marker of parenteral protein tolerance in VLBW and ELBW infants is not useful [35, 31, 36]. Ridout et al reviewed 121 preterm infants less than 1250 g on total parenteral nutrition in the first 72 hours of life and found no correlation between amino-acid intake and serum BUN concentration [41]. Further study is needed to define markers of protein tolerance and accretion in premature infants.

Fat

Intravenous lipid contains triglycerides (soybean oil or safflower oil), egg yolk phospholipid (for emulsification) and added glycerol to achieve isotonicity. It is an energy dense solution and available in 10 and 20% concentrations. Lipid supplements provide approximately 2 kcal/mL (20% solution). Infants tolerate 20% solution better because of lower phospholipid to triglyceride ratios. Fat should provide 25-40% of non-protein parenteral energy [15, 16]. Available parenteral lipid solutions in the US are soybean oil based. Soybean oil is rich in the omega-6 PUFA, linoleic acid. Its metabolites, especially peroxides (oxidative stress) may induce toxic effects and they also promote release of proinflammatory cytokines (eicosanoids). However, studies do not show increase risk of bacteremia or fungemia while receiving soybean oil based lipid emulsion [46, 47, 48]. Commonly used fat emulsions in United States are Intralipid® (Sigma Aldrich, St Louis, MO, USA) and Liposyn® (Hospira, Lake Forest, IL, USA) in 20% solution. Most authors recommend starting with 1-2 g/kg per day of lipids on the first day with step wise increments of 0.5 to 1 g/kg per day up to 3 g/kg per day of maintenance for premature infants [45, 50]. Lipid particles of intralipid solution are metabolized by lipoprotein lipase whose activity is reduced in preterm infants, especially less than 28 weeks' gestation [51]. Therefore, assessment of tolerance should be done by frequent monitoring of triglyceride levels. Current consensus is to keep triglyceride level <200 mg/dL. A dose reduction of intralipid infusion should be considered with triglyceride level >250 mg/dL in premature infants, but minimum supplementation of lipid is always required to prevent essential fatty acid deficiency. Linoleic and linolenic acids cannot be synthesized in the body and are considered essential fatty acids. Biochemical evidence of essential fatty acid deficiency can be observed within 72 hour of birth with an elevated Triene to Tetraene ratio [>0.4] [52]. This clinically manifests as hemorrhagic and scaly dermatitis, impaired growth, visual disturbances and hypertension. Studies have shown that

early supplementation of lipid is safe and well tolerated in premature infants and associated with better weight gain and improved nutritional support [53, 54].

Electrolytes

As described earlier, preterm infants has higher TBW (total body water) content, with most in the extracellular compartment. During the transition period after birth (especially first 3-5 days of life), extracellular compartment should contract which is characterized by initial period of oliguria followed by diuresis. Fluid supplementation during this period of physiologic change should be based on ongoing losses (including insensible which may be high in VLBW and ELBW infants) and urine output. Careful monitoring of serum electrolytes and body weight is essential. Fluid and nutritional supplementation should be sequentially increased (around 140 ml/kg per day) to provide energy and achieve growth [50]. Preterm infants do not require sodium and potassium in TPN during the transition period after birth. The requirement of sodium, potassium and chloride after the period of diuresis is 2 to 4mEq/kg/day; 1-3mEq/kg/day; 2-4mEq/kg/day, respectively [55].

Table II. Parenteral vitamin solution

Vitamin	Amount per 5 mL
Ascorbic acid (Vitamin C)	80mg
Vitamin A (retinol)	2300 USP units
Vitamin D	400 USP units
Thiamine (vitamin B1)	1.2 mg
Riboflavin (vitamin B2)	1.4 mg
Pyridoxine (vitamin B6)	1.0 mg
Niacinamide	17.0 mg
Dexpanthenol	5 mg
Vitamin E	7.0 USP units
Biotin	20 mcg
Folic acid	140 mcg
Vitamin B12	1.0 mcg
Vitamin K1	200 mcg

[a] MVI Pediatric is a lyophilized, sterile powder intended for reconstitution and dilution in intravenous infusion. Infuvite pediatric is supplied as a 4 mL and 1 mL via that may be combined for administration. For each vitamin mixture, 5 mL of reconstituted product supplies the indicated amounts of the vitamins [56].

Calcium and phosphorus deserves detailed discussion for preterm infants, as inadequate supplementation results in poor bone mineralization which manifest clinically as osteopenia and even rickets. The presentation of bone disease in this population varies from clinically silent disease to fractures and full blown rachitic bone changes. An inadequate supply of nutrients (vitamin D, calcium and phosphorus), prolonged periods of total parenteral nutrition, immobilization and the intake of some drugs (e.g. diuretics, steroids) are contributory to this pathogenesis [57]. High alkaline phosphatase and low serum phosphorus level has 100% diagnostic sensitivity and 70% specificity for bone disease of prematurity [58]. It is essential to provide optimal calcium and phosphorus while an infant is on TPN, but it is challenging because of solubility issues. Many factors affect the solubility of calcium and phosphorus in TPN such as, pH, type and concentration of AA, calcium-phosphorus ratio, and type of calcium salt. The fetus accrues the highest amount of calcium and phosphorus in the last trimester of pregnancy at a rate of approximately 120 mg/kg/d and ~60 mg/kg/d, respectively [59, 60]. Currently, it is not possible to provide enough calcium and phosphorus in TPN to support optimal bone mineralization.

The addition of cysteine in AA solution lowers pH of the TPN solution and improves calcium and phosphorus solubility. The ideal calcium: phosphorus ratio to promotes highest retention is 1.3-1.7: 1 [12, 46]. Magnesium, which is mainly an intracellular cation, is also essential for bones and teeth structure. It acts as a cofactor for multiple enzymes in the body, including binding to ATP for kinase reactions, and affects permeability of excitable membranes and neuromuscular transmission. Magnesium rarely requires any adjustment in TPN. Current recommendation of calcium, phosphorus and magnesium supplementation in TPN is 60-100 mg/kg/day; 50-80 mg/kg/day and 6-10 mg/kg/day respectively [19, 61].

Vitamins and minerals

Currently, two multivitamin (MVI) solutions for TPN are available in the US. MVI Pediatrics[a] (AstraZeneca pharmaceuticals, Westborough, MA, USA) and Infuvite Pediatrics (Boucherville, Quebec, Canada).

The recommended dose is 40% (2mL) of the currently available reconstituted single dose (5mL) of the MVI mixture. *However, there are no products currently available specifically for preterm infants*. The American Academy of Pediatrics [56] recommends adding 2 ml/kg/day of currently available multivitamin solution (not to exceed more than 5ml) to TPN. Provision of adequate amount of vitamin A in TPN is a significant challenge as it lost through photo degradation and absorption to plastic tubing and solution –containing bags, and this may be particular concern using long term TPN.

Trace minerals are necessary for various enzyme activities, lipid and protein metabolism and antioxidant activities. Zinc and selenium are needed in TPN soon after birth for premature infants. Zinc has an important role for many enzymes functions and is essential for growth and tissue differentiation. Zinc deficiency is a common problem in infants and children, which may manifest as poor growth, increased risk of infection and skin rash [62] for which care provider must be vigilant for. Selenium is an essential component of glutathione peroxidase, an important antioxidant enzyme. Studies have shown an association with selenium deficiency and bronchopulmonary dysplasia [63]. Griffin et al [64] suggested parenteral iron requirements for VLBW infants would be 0.2 to 0.37 mg/kg/day per factorial calculation [64]. Iron is best provided enterally, which should be started at 2-6 weeks of age; however if the preterm infant requires prolonged parenteral nutrition, iron should be added in TPN. Iron supplementation at 2 mg/kg per day from 6 weeks to 6 months has shown to reduce the risk of iron deficiency anemia effectively, with no short term adverse effects on morbidity or growth [65]. A study by Friel et al [66] has shown no advantage of higher iron intake than current recommendations in low birth weight infants in terms of cognitive outcomes. Carnitine derives from lysine and methionine and is essential for fatty acid transport through mitochondrial membrane for oxidation. Premature infants on TPN have low carnitine levels; however meta-analysis of carnitine supplementation studies showed no evidence of effect on ketogenesis, lipid utilization or weight gain [67].

Side effects and/or complications

Besides nutritional benefits, total parenteral nutrition has its own complications. Most neonatal ICUs favor using central lines in premature infants for TPN delivery than peripheral line. See table III for additional TPN complications.

Table III. Complications of total parenteral nutrition

Acute	Chronic
Metabolic complications	Systemic complications
Hypoglycemia	Parenteral nutrition associated liver disease
Hyperglycemia	Metabolic bone disease
Metabolic acidosis	
Hypophosphatemia and other electrolytes imbalance	
Hyperlipidemia	
Mechanical complications (Central line related)	Infectious complications
Extravasation and tissue necrosis	Bacterial infections especially Staphylococcal species
Infiltration	Fungal infections: Candida species, Malassezia furfur
Thrombosis	
Pleural or pericardial effusion	
Cardiac arrhythmia from malposition of catheter	

Adapted from P. Patel, J. Bhatia [68]

Aluminum is a contaminant in all parenteral nutrition (PN) solutions. Bishop et al showed prolonged use of TPN containing aluminum is associated with adverse neurodevelopmental outcome in premature infants [69]. Products with low aluminum content should be used in neonates in order to prevent potential adverse effects in these vulnerable premature infants [55]. Though, multivitamins preparation in TPN are the major contributor to generation of free radicle with exposure to light, intravenous lipid also undergoes peroxidation with light exposure especially phototherapy [71, 72]. While on TPN, frequent electrolyte measurements should be done in order to prevent acute metabolic derangements. Extravasation and tissue necrosis is more frequently seen when TPN administered using a peripheral line. Daily careful inspection of the TPN infusion site might help to initiate early treatment in case of extravasation of TPN.

A major complication of prolonged TPN is cholestatic liver disease (CLD), and its risk factors are duration of parenteral nutrition, prematurity and delayed enteral feeding [73, 74]. Other contributory factors for CLD include parenteral intralipid (especially soybean oil based emulsion) administration, recurrent sepsis and photo oxidation of parenteral nutrients [71]. Incidence of CLD is as high as 60% in premature infants on prolonged TPN (>100 days) [74, 75]. Fish oil based lipid emulsion is a novel approach for treatment of CLD and results are promising, but it is not available in the US currently. However, studies have shown fish oil based emulsions are superior to mixed lipid emulsion and soybean based emulsion in treatment of CLD. Also, newer mixed lipid emulsions (SMOF: mixture of soybean oil, MCT, Olive oil, and fish oil) are well tolerated by premature infants and effective in optimizing fatty acid profiles, improving direct bilirubin level (a marker of CLD) and reducing liver injury in case of parenteral nutrition associated liver disease [79, 80].

Systemic infections remains a major cause of morbidity and mortality for premature neonatal population because of immature immune system. Central lines are the definite risk factor for invasive systemic infection (CLABSI) and account for up to 70% of all hospital-acquired blood stream infection for premature infants [76]. Use of 'bundled' interventions including staff education on care and maintenance of central lines, hand hygiene, strict adherence to unit policy and removal of central lines as soon as not needed, help to decrease the rate of CLABSI [77, 78].

Conclusions

As preterm infants are at risk of extra uterine growth restriction, early and optimal parenteral nutrition is essential in neonatal intensive care units. Careful and gradual advancement of protein, carbohydrate and lipids in the TPN is the key for providing optimal energy and achieving appropriate post-natal growth. For infants in whom fluid restriction is medically necessary (e.g. extreme prematurity, bronchopulmonary dysplasia, congenital heart disease), use of standardized concentrated PN [SCAMP], which does not compromise infants energy intake, has shown to improve growth status especially, head growth [43]. CLD is serious and common complication of long term TPN usage. Initiation and maintenance of the enteral feedings is of paramount importance which helps gut maturity and has a significant role in treating CLD. Use of SMOF lipid mixture as well as fish oil emulsions have shown to improve TPN cholestasis (a major factor in PNALD) compared to currently available soybean based oil lipid emulsion. CLABSI remains a major challenge in neonatal ICUs for infants on prolonged TPN. A collective approach that includes health care professionals and NICU staff with strict unit policy implementation might help to lower the incidence of CLABSI, as it has an impact on neonatal morbidity, mortality and health care costs.

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