Review of Macronutrients in Parenteral Nutrition for Neonatal Intensive Care Population

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ABSTRACT

Parenteral nutrition (PN) has become essential in the management of sick and growing newborn populations in the NICU. In the past few decades, PN has become fundamental in the nutritional management of the very low birth weight infant (<1,500 g).[1] Although the components in PN are commonly determined and ordered by the physician or neonatal nurse practitioner provider, the NICU nurse is responsible for confirming the components in the daily PN prior to infusion and is responsible for maintaining the infusion of PN. Nurses should understand the nutritional components of PN as well as the indications, side effects, and infusion limitations of each component. The purpose of this article is to review the macronutrients in PN, including carbohydrates, protein, and fat. A subsequent article will review the micronutrients in PN, including electrolytes, minerals, and vitamins.

Keywords: total parenteral nutrition (TPN); nutrition; macronutrients

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TOTAL PARENTERAL NUTRITION (TPN) was introduced in the 1970s to manage nutritional needs of newborns with short bowel syndrome. Although newborns requiring long-term TPN are primarily limited to those with anatomic or functional gut abnormalities (i.e., bowel obstructions, gastroschisis, short bowel syndrome, necrotizing enterocolitis, alterations in gut perfusion), parenteral nutrition (PN) has become essential in the management of sick and growing newborn populations in the NICU. In the past few decades, PN has become fundamental in the nutritional management of the very low birth weight (VLBW) infant (<1,500 g).[1] Although the components in PN are commonly determined and ordered by the physician or neonatal nurse practitioner provider, the NICU nurse is responsible for confirming the components in the daily PN prior to infusion as well as for maintaining the infusion of PN. Nurses should understand the nutritional components of PN and also the indications, side effects, and infusion limitations of each component. The purpose of this article is to review the macronutrients in PN, including carbohydrates, protein, and fat. A subsequent article will review the micronutrients in PN including electrolytes, minerals, and vitamins.

OVERVIEW OF PARENTERAL NUTRITION IN THE NICU

Safe administration of PN in the NICU is the goal, and yet directing the composition of individualized PN is complex. The NICU population including the critically ill newborn, the VLBW, and the extremely low birth weight (ELBW) newborns are among the highest-risk patients, susceptible to injury from medical error because of their small size, narrow therapeutic range, specialized needs, developmental limitations, and low tolerance for pharmaceutical errors.[2,3] These fragile newborns are also dependent on adequate and early nutrition to prevent the effects of progressive intrauterine growth restriction, acquired postnatal growth restriction, and damaging catabolism at a time when growth promotion and healing are paramount to minimizing morbidity and mortality. The goal of PN is to support the

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newborn's ongoing metabolic and energy needs, prevent catabolism of protein stores for energy, replenish or establish glycogen and fat stores, and promote growth and neurodevelopmental outcome. In newborns who are unable to meet their nutritional needs with enteral feedings, the aim of PN is to promote growth at rates comparable to well fetuses or newborns of comparable age.[4–6] The macronutrients in standard PN solution are carbohydrates and protein. Fat is the third macronutrient provided with the addition of a lipid emulsion infusion. It must also be recognized that water is an essential nutrient, and providing adequate fluid to meet daily requirements is fundamental to adequate nutrition.

CARBOHYDRATES IN PARENTERAL NUTRITION

The carbohydrates in PN are provided as monosaccharides in the form of dextrose, and the required concentration is commonly 5–15 percent dextrose in water to deliver a glucose infusion rate (GIR) of 3–12 mg/kg/minute of glucose. Glucose is utilized at increasing rates for decreasing gestation; therefore, preterm newborns synthesize glucose at a rate of about 6–8 mg/kg/minute, whereas term newborns synthesize glucose at a rate of 3–5 mg/kg/minute.[7] The glucose requirements will therefore have a wide range depending on the individual needs of the newborn. Glucose is the main source of energy for the fetus in utero, and after birth it is the primary source of energy required by the developing brain because it is readily metabolized.[8] Newborns and especially premature newborns have limited glucose stores in the form of glycogen, and they also have metabolically active organs dependent on a continuously available glucose supply for energy. In the absence of an exogenous glucose source, any energy reserves are rapidly depleted after birth, especially in the sick or immature newborn. This results in catabolism of endogenous protein, which, in turn, causes a negative nitrogen balance that may be difficult to reverse or replenish and which could have lasting effects on growth and development potential.[9–11]

Understanding the energy requirements of the neonate is essential for prescribing PN. The estimated resting metabolic rate in a neonate receiving PN and maintained in a neutral thermal environment is 40–60 kcal/kg/day. The neonate requires an additional 3–4.5 kcal/kg of weight gain for growth or an additional 45–67 kcal/kg above the caloric needs for resting metabolic rate. Therefore, if the desired weight gain is 15 g/kg/day, then the neonate requires 85–127 kcal/kg/day. This estimate reflects calculations for healthy growing preterm infants at three to four weeks of age. Sick and ELBW infants have additional metabolic demands that have yet to be defined but would increase the caloric needs for weight gain growth.[5,12]

Most infants will receive adequate carbohydrate substrate with a GIR of 3–5 mg/kg/minute, but VLBW and ELBW infants with characteristic morbidities will need up to 12 mg/kg/minute to maintain sufficient energy for metabolism; however, some providers increase the carbohydrate load to a GIR of 14–15 mg/kg/minute for additional calories. GIR in excess of 15 mg/kg/minute may exceed the ability of most infants to oxidize glucose and may promote lipogenesis. Lipogenesis is inefficient, using energy to store fat. It is also associated with increased susceptibility to infection. An additional side effect of providing excess glucose is the risk of hyperglycemia.[5,13,14]

The risk of hyperglycemia increases with decreasing gestational age and may interfere with meeting the newborn's nutritional goals in the first few weeks of life. The etiology of hyperglycemia in the newborn is usually multifactorial and includes ineffective insulin secretion, end organ insulin resistance, decreased glucose intracellular transporters, elevated catecholamines and glucocorticoids altering glucose metabolism by stimulating glucose production and limiting glucose utilization, absence of enteral stimulus for insulin secretion, and excess glucose infusions.[6] Early amino acid (AA) administration may reduce the risk or severity of hyperglycemia by stimulating endogenous insulin secretion.[15] Lipid infusions may also reduce the risk, but in some infants lipid infusions may contribute to the severity of hyperglycemia. Presumably, this is because of increased plasma free fatty acid (FFA) concentrations that decrease peripheral glucose utilization and inhibit the insulin effect, resulting in increased glucose concentrations in the plasma.[16] The combined administration of AA and a lipid infusion promote gluconeogenesis, spare glucose utilization, and stimulate insulin release.

Neonates with hyperglycemia require restricted dextrose infusions until they are better able to tolerate the minimum requirements for resting metabolic rate; however, restricted carbohydrate will impede growth. Insulin infusions are not optimal for management of hyperglycemia in the ELBW infant because insulin may reduce protein synthesis and growth potential and may result in lactic acidemia.[15,17] However, insulin infusions may be required if hyperglycemia persists with minimal GIR or if serum glucose levels exceed 200–250 mg/dL (11.1–13.9 mmol/L).[18] Close monitoring for hypoglycemia is essential if insulin infusion is required and should prompt evaluation for serious morbidities including sepsis and intraventricular hemorrhage. Weight gain during the period of an obligate reduction in carbohydrate infusion, when the neonate is not receiving adequate calories for growth, is usually because of increases in total body water weight and not growth weight.

PROTEIN IN PARENTERAL NUTRITION

The protein source of TPN is 10 percent TrophAmine, a crystalline AA hydrolysate with elevated ratios of essential to nonessential AAs that promote endogenous production of the branch AA, leucine, isoleucine, and valine. Reduced stability and solubility of the AAs prevents the optimization of AA preparations. Cysteine, the substrate for the important antioxidant tripeptide glutathione, is routinely added to PN to prevent cysteine deficiency that may impair protein synthesis.[5,15,19] The recommended daily dose of cysteine added to PN in the neonate is ~100 mg or 30–40 mg/g of AA.[5,20]

The AA hydrolysate is generally ordered in g/kg/day with a common range of 3–4 g/kg/day, providing an adequate exogenous protein source to prevent catabolism of endogenous protein stores and promote lean body mass growth. Term newborns without increased requirements for healing require 3 g/kg/day, and the VLBW preterm newborn requires 4 g/kg/day. It was thought the daily AA needed to be advanced gradually; however, the evidence indicates that newborns tolerate early administration of AA and require little or no time to acclimate to the parenteral protein.[21–23] Furthermore, preventing negative nitrogen balance from DOL 1 is optimal because replacing nitrogen deficits incurred when inadequate protein is provided for even one or two days may not be possible and may lead to irreversible deficits in brain growth.[7,21,24–27] The equivalent protein loss without protein intake is 0.5–1 g/kg/day in VLBW newborns and likely greater in ELBW newborns without protein supplement in the first few days up to 1.1–1.5 g/kg/day with only a 70 percent protein retention.[6,28] In addition, even if adequate protein is given, minimal energy needs must be met with carbohydrate and lipid intake at 50–90 kcal/kg/day to insure adequate nitrogen retention and positive nitrogen balance with infusion of adequate AA in PN.[29,30]

The side effects of aggressive AA supplementation in PN, especially in the ELBW infant, were presumed to include azotemia, hyperammonemia, and metabolic acidosis.[31,32] These complications described with casein hydrolysate preparations of intravenous AA have not been associated with crystalline PN solutions. The development of these abnormalities is not a reflection of AA infusion intolerance but instead reflects the complex management of hydration, renal immaturity, energy intake, perfusion, and acute comorbidities of immaturity.[5,33] Prolonged exposure to the AA solution in PN has been suggested as contributing to parenteral nutrition associated liver disease (PNALD) and cholestasis, but this association occurs in neonates receiving taurine-deficient AA preparations designed for adults. Taurine conjugation of bile acids protects the liver from hepatotoxic glycine-conjugated bile acids.[34]

There are other factors or components in PN that may contribute to PNALD, including the chemical composition of the tubing, the trace elements, and aluminum toxicity, but there is limited evidence for direct cause-and-effect implications for most of these factors.[34] The gradual addition of early enteral feedings reduces the risk of bile stasis that may contribute to cholestasis, but the degree of liver immaturity, sepsis, and presence of short bowel syndrome as well as the infusion of soy-based lipid emulsions are all predisposing factors contributing to the risk of PNALD.[34]

LIPID EMULSION FOR PARENTERAL NUTRITION

The addition of 20 percent lipid emulsion infusion at 1–3 g/kg/day provides a low osmolar fat source for energy to achieve and maintain a positive energy balance after birth. Fat is one of the main energy sources after birth, especially for VLBW and ELBW infants, providing for metabolic fuel and fat deposition.[8]

Lipid emulsions provide the high energy content important in PN, sparing dietary protein for growth. Lipid infusions provide essential fatty acids for targeted tissue growth as well as specialized cell reproduction, metabolism, and regulation in the cells of the brain, intestine, and retina. These essential fatty acids are also important in the production of prostaglandins and platelets.[21,35] In the United States, the available lipid emulsion for PN is a 10 percent or 20 percent soy-based emulsion. The 20 percent emulsion is preferred because it does not promote the hyperphospholipidemia that is a side effect of the 10 percent emulsion, which has high phospholipid content.[19] The minimum dose of lipids to prevent essential fatty acid deficiency (EFAD) is 0.5–1.0 g/kg/day or at least 4 percent of caloric intake.[6] EFAD can occur as early as the second day of life in the premature newborn not receiving supplemental essential fatty acids.[19,36,37] EFAD may manifest in a week without essential fatty acids, with the development of scaly skin lesions or dermatitis, thrombocytopenia, and poor growth. Visual and neurologic abnormalities are potential consequences of EFAD in infants receiving PN without essential fatty acids.[5,6]

The rate of lipid clearance is determined by each infant's ability to metabolize/hydrolyze fat. Ideally, lipids are infused over a 24-hour period to maximize clearance. Lipid infusion rates that exceed the rate of fat hydrolysis will result in excess concentrations of plasma triglycerides and FFAs. Although there is no consensus on the maximum triglyceride level for VLBW or ELBW infants, a triglyceride level of 250 mg/dL (28.2 mmol/L) is the highest level accepted in the literature.[5,8] FFA levels may be a preferred measure of lipid tolerance, but that test is not routinely available. Based on a small observational study that could not discount confounding variables including sepsis and exposure to steroids, excess FFA levels were implicated in displacing bilirubin from albumin binding sites in infants less than 28 weeks.[38,39] Excesss FFA levels have also been implicated in altering pulmonary function and free radical release, again without confirmed well-controlled studies.[40,41] Nevertheless, adequate and early lipid infusion optimize nonprotein energy intake with PN and prevent EFAD, with the benefits outweighing the potential risks.[6,42]

Long-term lipid infusions with PN may contribute to associated liver disease. It is likely the soy-based lipid emulsion used in the United States is more suspect because these preparations contain omega-6 fatty acids. Omega-6 fatty acids have proinflammatory effects that may impair triglyceride transport and contain phytosterols that reduce bile secretion.[34] An alternative lipid emulsion that has not been approved for use in the United States is prepared from fish oils. It is less liver toxic because it has omega-3 fatty acids, which have anti-inflammatory properties in contrast to the omega-6 fatty acids in the soy-based lipid emulsion currently used. It can be used with U.S. Food and Drug Administration (FDA)

compassionate approval to treat cholestasis but may be the future fat emulsion for PN pending full FDA approval.[5,43,44] The potential for PNALD is greatest without enteral feedings, with short bowel syndrome and long-term TPN.

It is common practice to advance lipid infusion incrementally over the first few days; however, the studies indicate aggressive advancement of lipid emulsion for PN to optimize energy source, like aggressive advancement in AA supplementation, reduces the risk of postnatal growth restriction and poor neurodevelopmental outcomes in VLBW and ELBW newborns.[26,27] No adverse effects have been associated with starting at least 1–2 g/kg/day of lipids immediately after birth with a target of 3 g/kg/day by as early as 24 hours[21]and at least by seven days.[8] Lipids are infused over 24 hours to maximize clearance and prevent variable and higher triglyceride concentrations.[15,45] Transient elevated triglyceride levels are associated with infusion of liposomal amphotericin B, steroids, and sepsis.[5,37] It is important to incorporate the daily lipid infusion volume into the fluid calculation, as 20 percent of lipid emulsion is 80 percent free water.

Monitoring Neonates Receiving Parenteral Nutrition

Given the goal of PN is to optimize growth, daily weight monitoring and at least weekly occipitofrontal circumference (OFC) and length monitoring are important indicators of the adequacy of nutrition. There is no consensus on laboratory monitoring in the literature, but most experts indicate that routine monitoring of glucose homeostasis and monitoring indices that indicate metabolic complications or alterations in nutritional and electrolyte status should be monitored. These indices would include serum electrolytes (sodium, potassium, chloride, and bicarbonate as well as calcium, phosphorus, and magnesium), renal function indices (blood urea nitrogen and creatinine), liver function indices (direct and total bilirubin, alanine and aspartate aminotransferases), and total protein, serum albumin, and triglyceride levels. The frequency of testing should be based on the status of the neonate, the presence of factors that may contribute to complications, and response to nutrition prescription of the PN. Once the neonate demonstrates tolerance of the nutrition prescription, weekly monitoring of electrolytes, renal function indices, and liver function tests with a complete metabolic panel along with at least daily glucose screening may be adequate unless complications present or anticipated growth is not achieved.[6]

ADDITIONAL CONSIDERATIONS FOR ADMINISTRATION OF PN

Unless the newborn presents with excess total body water weight at birth as with hydrops, the birth weight is used to calculate weight-dosed PN macronutrients as well as the micronutrients until the birth weight is surpassed by growth. Weight from edema would not be considered growth weight and would not be used to calculate PN needs. Often, PN is infused as a supplement to slowly advancing enteral feedings. As such, the components are calculated for the current weight, and the enteral feedings, if tolerated, are subtracted from the hourly PN infusion. If the PN is ordered as if the newborn is not feeding, then the components and volume will be calculated for the 24-hour requirement. In that way, if the anticipated enteral feeding is not tolerated, the PN infusion will be adequate in volume and composition. Otherwise, the concentration of components ordered in the reduced 24-hour PN volume, after subtracting the expected enteral intake, may exceed both the recommended amount of components per volume and the osmolality and potentially affect the chemical compatibility of the solution. There may be a nutritional benefit to increasing the protein in PN when approaching a daily intake of half PN and half-enteral feedings; however, there is no available evidence. This could potentially prevent reduced protein intake prior to reaching optimally fortified enteral intake.

Intravenous access is important in determining PN components because the dextrose and protein contribute to osmolality of the PN. The flow rate and diameter of peripheral veins limit tolerance of infusions with osmolality in excess of 600 mOsm or pH <5 or >9.[46]

Central venous access in the inferior vena cava (IVC) or the superior vena cava (SVC), via placement of a percutaneous central venous catheter (PCVC), is ideal for PN infusions. Insertion of PCVC, or percutaneous insertion of central catheter lines in vessels with larger diameters and greater flow, as with insertion in the IVC or SVC, optimizes hemodilution of the potentially hyperosmolar or irritating PN infusate. Hemodilution of PN infusion will minimize if not prevent damage to the endothelial lining and tunica intima of the vein, which is associated with phlebitis, chemical erosion, and infiltration. The acidity of the PN infusate may result in chemical damage to the vein, which also leads to phlebitis.[46] PN solutions are acidic to enhance electrolyte solubility. Calcium and phosphorus will precipitate at increased pH levels greater than 6, but the safe pH range is narrow with many confounding variables.[47] These tend to be the most unstable of the electrolytes, but electrolyte solubility is a common challenge when compounding PN.

Free water is an important component of nutrition. Neonates require adequate free water to replace sensible losses (urine, stool, gastric, cerebrospinal fluid, thoracotomy, and peritoneal losses) and maintain adequate hydration. Fluid needs in the newborn are postnatal and gestational age dependent. The minimum fluid requirements are usually 60–80 mL/kg/day on the first day of life in the neonate who is not being fed, but this may be in excess of 100 mL/kg/day in the ELBW infant. Fluid needs increase over the first five to seven days to 150 mL/kg/day, but the insensible water losses (evaporative losses from skin and respiratory tract) as well as insensible water gains or lack of anticipated sensible losses need to be considered for each neonate.[48] For most newborns, the first week or two of life in most newborns and

longer in ELBW newborns, appropriate fluid adjustments are based on daily weight changes, which usually reflect changes in total body water. Serum electrolyte trends during these early weeks are also affected by total body water changes.[49,50]

SUMMARY

PN is essential to optimize nutrition in the NICU population and especially the VLBW or ELBW neonates until adequate enteral intake can be achieved. Most neonates both tolerate and benefit from fairly aggressive macronutrient advancement after birth to prevent the deficiencies in energy and protein that are difficult to reverse. Adequate nutrition is essential for growth and development. The administration of PN with adequate carbohydrates and fat for energy, sufficient AAs for growth, and sufficient fluid to prevent deficits and promote growth will improve the potential outcome of the most fragile neonates.

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