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Parenteral nutrition in the neonate

L.K.R. SHANBHOGUE
From the University Department of Paediatric Surgery, Alder Hey Children's Hospital, Liverpool.

The newborn infant may be a full term infant, premature baby or small for gestational age. In view of the characteristic metabolic changes that occur in a newborn, emphasis in this review will be on total parenteral nutrition (TPN) in a neonate. It should, however, be emphasised that enteral approach is the preferred route for nutritional support and TPN is used only when the gut is unavailable for a long period.

The normal full term infant has a gestational age of more than 38 weeks and a birth weight of greater than 2500 g. Although full term infants are born with adequate energy reserves in the form of glycogen and fat, they do not tolerate fasting periods in excess of four to six hours without developing hypoglycemia.

Premature infants are those born before 38 weeks. The main features of prematurity are red thin skin, soft malleable ears, absence of breast tissue, and undescended testicles or relatively enlarged labia minora and clitoris. Apnoeic episodes, hypothermia, hypoglycemia are common in these infant. They are more prone to intraventricular hemorrhage, and their retinae and lungs are susceptible to high oxygen levels.

Small for gestational age babies are those who have a gestational age of more than 38 weeks, but, weigh less than 2500g. They are small mainly as a result of some form of intrauterine growth retardation. These infants tend to have polycythemia. Relative lack of body fat and glycogen leads to episodes of hypothermia and hypoglycemia.

Address for reprints: Mr.L.K.R. Shanbhogue
Institute of Child Health Alder Hey Children's Hospital
Eaton Road Liverpool L12 2AP United Kingdom

Throughout the final trimester of pregnancy there is a rapid accretion of nutrients in the fetus combined with major changes in body composition. The growth rate is rapid and the body weight of the fetus more than doubles from 28 weeks gestation (1200 g) to 40 weeks gestation (2500 g). The aim of parenteral nutrition in a premature infant will be to simulate intrauterine growth rates whilst at the same time minimising the stress to the immature metabolic system.

In the early stages of gestation fetus lays down no fat. Fat content increases gradually from 3.5 % at 28 weeks to 15 % at 40 weeks. Fat is the major source of stored energy both in an adult and a full term neonate. In a 70 kg adult it amounts to 141000 kcal while in a newborn with a body weight of 3500g, it amounts to 4800 kcal.

Glucose is stored as glycogen, and glycogen stores are always very small when compared to that of fat. Glycogen synthesis begins in the fetus mainly during last two months of gestation. Liver glycogen stores alone provide sufficient energy in a term infant for 4-6 hours of postnatal life. Premature and small for gestational age infants have minimal stores of glycogen in their liver and with an immature gluconeogenetic system, hypoglycemia can occur very rapidly without dextrose infusion.

Most of the minerals and vitamins accumulate gradually throughout the gestation except for calcium and phosphate. More than half of total fetal calcium and phosphate tend to accumulate during last four weeks of gestation, which is also coincident with the preiod of rapid ossification of the fetal bones.

In summary, a premature infant has excess of to-

tal body water and minimal stores of fat and glycogen and can not tolerate starvation without catabolising the lean tissue.

Nutritional Assessment

The object of nutritional assessment is to detect and categorize patients with different degrees and types of malnutrition and relate these to the risk of morbidity and mortality [1]. It is of utmost importance to distinguish betwen two principal forms of protein energy malnutrition, marasmus and kwashiorkor. The host immune response is seriously impaired in hypoalbuminemic malnutrition (kwashiorkor) accompanied by increased morbidity and mortality. This immunological impairment is usually minimal in a patient with marasmus.

In most instances the history and clinical grounds will be enough to initiate total parenteral nutrition. It is obvious that any neonate, particularly premature, who can not maintain satisfactory oral intake for more than three days will need nutritional support. This will include neonates with necrotising enterocolitis, gastroschisis,short gut syndrome, extreme prematurity, intractable diarrhoea, and whenever there is any delay in bowel function following gastrointestinal surgery [2].

Weight, length, head circumference, triceps skinfold thickness (TSF), mid arm muscle circumference (MAMC), serum albumin level are perhaps the most practical variables for nutritional assessment in a neonate. Creatinine height index, serum transferrin, and prealbumin are additional useful variables.

TSF and MAMC provide an estimate of body fat reserves and muscle mass, respectively. The MAMC is a more sensitive measure of protein nutrition even in presence of excess of total body water, as fluid does not tend to accumulate to the same degree in the arm. These also serve as useful baseline values, should the patient need long term nutritional support.

Serum albumin (half life of 20 days) has been classically used as an indicator of malnutrition. Hypoalbuminemic malnutrition is characterized by depletion of visceral protein mass. The measurement of visceral proteins such as serum albumin and transferrin is an attempt to define that a decrease in the serum concentrations of these proteins is a consequence of decreased liver biosynthesis, which in turn is due to limited supply of the substrates because of malnutrition and an actual decrease in organ mass.

Serum transferrin has a shot half life (10 days), but, affected by many factors other than malnutrition. Prealbumin in turn has extremely short half-life (2 days), but, it appears to be a better indicator of recent dietary intake rather than nutritional status. Retinol binding protein has a half life of 12 hours and its value in nutritional assessment appears to be similar to that of prealbumin [3].

Several investigators have demonstrated creatinine excretion in children and adults to be a good predictor of lean body mass using research techniques such as 42K dilution, 40K total body counting or total body water as a measurement of lean body mass. Creatinine excretion in patients with malnutrition is reduced and no longer correlates with body weight, but, continues to correlate with lean body mass. Since height is not appreciably affected by malnutrition, the creatinine height index affords a useful technique to assess lean body mass. Nevertheless, it is important to consider factors that alter creatinine excretion suh as creatine free diet, trauma, sepsis and acute renal failure.

Nutritional Requirements

Energy

In a neonate, basl metabolic rate accounts for 34-50 kcal/kg/day. Intermittent activity and occasional cold stress need 25 kcal/kg/day. Specific dynamic action uses up 8 kcal/kg/day. In neonates on oral intake, allowance should be made for 12-18 kcal/kg/day of fecal loss of calories. Furthermore, about 25 kcal/kg/day should be provided for growth. Considering the above factors a neonate needs 80-125 kacl/kg/day depending on

the maturity. Premature infants need calories in the upper range. It is important to realise that there is a coefficient of variation of approximately 15 % for these mean values [4].

The effect of surgery, trauma, burns and sepsis on energy requirements is not well understood in children. It is likely that some increment will be needed, particularly in cases of trauma and burns, but, may not be ask great as originally thought. It is also important to appreciate that a neonate maintained in thermoneutral zone has minimal cold stress and a ventilated neonate has no metabolic cost of breathing. Furthermore, in catabolic states there may not be any growth occurring, thus, further reducing energy requirements. In a recent study, critically ill infants were found to have a mean measured energy expenditure of less than 50 kcal/kg/day. In complicated cases measurement of actual energy expenditure using an indirect calorimeter is recommended.

Substrates

Glucose

Glucose is an essential fuel for the human newborn infant. Apart from other obligatory glucose-consuming organs (erythrocytes, renal medulla and cardiac tissue), glucose is the most important substrate for brain metabolism, and a continuous supply of this fuel is essential for normal neurological function. It is a source of energy even in the absence of oxygen through anaerobic glycolysis. Exogenous supply of gloucose within few hours after birth is essential in a premature infant who has minimal stores of fat and practically no glycogen reserves.

Dextrose, so called because of the dextrorotatory position of the glucose molecule, is the most commonly used carbohydrate for paretreral nutrition in infants. Each gram of hydrous dextrose provides 3.4 kcal. Dextrose infusions are well tolerated if the initial rate of administration does not exceed the hepatic rate of glucose production (6 to 8 mg/kg/min). Isotopic and indirect calorimetric studies have demonstrated that there is a limit to the amount of glucose that can be directly oxidised to meet the individual energy needs. In adults it is 4-5 mg/kg/min. Administration of excess glucose even with insulin may enhance glucose clearance rates but not oxidation rates. In neonates, oxidative glucose disposal rate is likely to be 7-12 mg/kg/min. Thus optimal amount of glucose in a neonate is 8-17 g/kg/day [5,6].

Administration of excess of glucose leads to lipogenesis. This is an energy consuming process and results in high respiratory quotient with increased carbon dioxide production, oxygen consumption and energy expenditure. Excess carbon dioxide production is of great significance in patients with limited respiratory reserve. Whenever there is difficulty in weaning a patient off the ventilator, a detailed analysis of substrates in TPN should be undertaken to ensure that excess of carbohydrate is not being infused [7]. The conversion to fat is also an energy-wasteful process and a reasonable alternative is a mixed fuel system using both dextrose and intravenous fat.

Protein

The usual source of protein is a standard synthetic amino acid solution containing a mixture of essential and nonessential amino acids providing 4 kcal/g. All the 20 amino acids used in protein synthesis should be available at the ribosomal level for optimal protein synthesis. Availability depends on amino acids released endogenously by breakdown of body proteins and amino acids supplied exogenously. All of the commercially available amino acid solutions contain eight known essential amino acids, but, there is a variation in the quantity and availability of nonessential amino acids. In a low birth weight neonate amino acids such as histidine, tyrosine, cysteine and taurine which are regarded as non essential become essential amino acids. However, there is no evidence to support that special amino acid solutions rich in taurine and cysteine, carry any advantage when compared to standard amino acid solutions. If a neonate is on long term parenteral nutrition care is required to monitor these amino acid levels to ensure against deficiency.

Growth and protein synthetic rates are much

higher in neonates than older infants. Therefore, a premature infant needs 3 g/kg/day of protein, full term neonates and older infants need 2.5 g/kg/day, while, children need 1.5-2 g/kg/day. To provide adequate utilisation of amino acids, atleast 150 nonprotein calories should be provided for every gram of nitrogen (6.25 g protein is equal to 1 g nitrogen). Pre-renal azotemia, hyperchloremic metabolic acidosis have been described in relation to synthetic crystalline amino acids and they are more likely due to excess of amino acids being given.

Lipid

Lipid emulsions are mainly polyunsaturated long chain triglycerides (LCT). The intravenous fat emulsions are manufactured from either soya bean or sunflower oil, stabilised with 1.2 % egg phospholipid and made isotonic, have high energy density, avoid excess carbon dioxide production, and contain essential fatty acids [8]. At 9 kcal/g of fat, a 10 % emulsion contains 900 kacal as fat, and an additional 200 kcal as density, avoid excess carbon dioxide production, and contain essential fatty acids [8]. At 9 kcal/g of fat, a 10 % emulsion cantains 900 kacal as fat, and an additional 200 kcal as glycerol and phospholipid, thus 1100 kcal/liter or 1.1 kcal/ml. A 20 %k emulsion contains twice the fat content, but the same glycerol content, thus 2000 kcal/liter or 2 kcal/ml.

The infused triglycerides are initially hydrolysed by lipoprotein lipase, an enzyme that is known to be activated by heparin. The resultant free fatty acids (FFA) circulate bound to albumin and follow two metabolic pathways: they either undergo beta-oxidation to acetyl-CoA, or are re-esterified to triglycerides and deposited in the adipose tissue. Acetyl-CoA in turn is oxidised in the citric acid cycle or used to form ketone bodies.

There is some evidence that LCT in excess of 50 % of calories, particularly in septic states, can cause impaired bacterial clearance, and may compromise neutrophil and reticuloendothelial system function. Lipid overload occurs when the rate of lipid infusion exceeds the capacity of capillary endothelial lipoprotein lipase to metabolise lipid emulsion triglyceride. Lipoprotein lipase activity is low in premature and small for gestational age infants. Activity of this enzyme is also known to be depressed in acute viral and bacterial infections. The excess lipid may coat or be engulfed by phagocytes and macrophages, interfering with their function. Thus preterm and small for gestational age infants should be closely monitored for lipid overload, and in infants with presence of sepsis, lipid should only be used in reduced dose.

The fat overload syndrome is caharcterised by hyperlipidemia, prolonged fever, hepatosplenomegaly, and spontaneous bleeding due to platelet dysfunction. Lipid emulsions are also known to reduce platelet adhesiveness. In a patient who develops bleeding problems or easy bruisability, lipid should be stopped.

Clearance of lipid emulsions from the circulatory system can be monitored by measurement of serum triglyceride levels, while the levels before initation of lipid therapy serve as baseline values. In the neonate, if the triglycredie concentration is 200-300 mg/dl or more during continuous lipid infusion, the rate and quantity of fat administered should be reduced. Additional methods which may be helpful in monitoring lipid clearance include measurement of FFA, cholesterol, as well as observation of plasma samples for turbidity.

FFA levels can often be elevated with lipid infusion. FFA in turn bind to serum albumin and in higher concentrations can displace free bilirubin. Therefore, in hyperbilirubinemic infants, lipid should be used in greatly reduced amounts or FFA/albumin ratio should be closely monitored.

Carnitine facilitates the transfer of long chain fatty acids across mitochondrial membrane for beta-oxidation. In its absence, beta-oxidation and thus cellular energy metabolism is impaired. Premature infants are born with relative inability to synthesise carnitine. Infants receiving long trem carnitine free TPN also have lower plasma carnitine levels. Thus, carnitine becomes a conditionally essential nutrient in a neonate on long term TPN.

A full term neonate can oxidise upto 4 g/kg body weight/day of lipid [6]. However, premature infants should be started on 2 g/kg/day which may be increased depending on their tolerance. In view of possible side effects of lipid emulsions in large doses, it is generally accepted that not more than 60 % of total calories should be supplied as fat.

We recommend that once total energy and protein requirements have been determined, equal amount of nonprotein calories be given as dextrose and lipid. Meanwhile, one should ensure that dextrose in not being given at a rate more than maximal oxidative glucose disposal and infused lipid is being satisfactorily cleared.

Trace minerals

Trace elements are present in the human body in trace quantities and are essential components of many enzyme systems in the body. Iron, zinc, copper, selenium, molybdenum, manganese and Iodide are the essential trace elemnts. If TPN is limited to less than four weeks and if one is certain of full oral intake subsequently, only zinc need be added [9]. Cause of trace mineral deficiency may be due to decreased storage as in a premature infant, increased utilisation as in rapid growth, or increased excretion. The most important mechanism, however, in the failure of clinicians managing the patient to provide sufficient amounts of the given mineral in the TPN infusion regimen.

It is essential to appreciate that excess of zinc can be lost in stomal losses, diarrhoeal stool or in urine if there is diuresis, and provide adequate supplementation. Zinc deficiency can manifest with hair loss and skin lesions resembling dermatitis.

Copper deficiency can manifest as osteoporosis, neutropaenia and iron-resistant microcytic anaemia. Selenium is an essential component of glutathione peroxidase, and its deficiency is known to be associated with fatal cardiomyopathy affecting children. While chromium is known to have a physiological role as a cofactor for insulin, its deficiency can be associated with carbohydrate intolerance [9].

It is a common practice not to add iron to TPN solutions when TPN is being given for a short term. Generally no iron supplements are necessary for the first month of life. However, the preterm infant is born with low iron stores and there may be further loss due to repeated blood sampling. Smaller doses of iron, 200 ugm/kg/day, will be necessary when TPN is given for a long time. Clinician should also be aware of hypoferremia of inflammation. This is a host response to infection or metabolic stress and results in low iron and high ferritin levels in the serum and it is not a state of iron deficiency. Free iron in the blood can facilitate bacterial proliferation [10]. Therefore, large doses of iron should be avoided, particularly when serum tarnsferrin is low. If large doses of iron is necessary, then blood transfusion may be preferable.

It should be emphasised that several trace elements regulate immune responses as well, particularly cell mediated immunity. Their deficiency can affect immunological functions of the host [11]. Every member of nutritional support team should also develop a habit of being trace mineralminded in response to any untoward clinical manifestations that might occur during the course of the TPN.

Vitamins

The major issues with lipid soluble vitamins are solubilising the vitamins in an aqueous solution, and avoiding potential toxic overdosage. Vitilipid* (Kabivitrum, Stockholm) is a preparation containing fat soluble vitamins (A,D,E and K). These vitamins are dissolved in soybean oil emulsion and emulsified with fractionated egg phospholipids in the same manner intralipid is prepared. Thus, infants are able to receive fat soluble vitamins with intravenous lipids. Aqueous solutions of these vitamins with a synthetic detergent such as polysorbate should be discouraged in view of questions about safety of such detergents in premature infants. It should also be emphasised that the minimum dose causing toxicity

of these vitamins has not been defined. However, in preterm infants, it is likely tahat atleast vitamin A needs to be supplied in a higher dose than recommended at present [9].

Water soluble vitamins function as cofactors for enzyme reactions, and needs for these vitamins are dependent on energy and protein content of the diet as well as energy utilisation. Daily provision is desirable as they are not stored to any significant extent. Although toxicity from water soluble vitamins is extremely unusual, there is potential for toxicity with large doses or with impaired excretion. Preterm infant may be particularly susceptible to these influences.

Peripheral intravenous nutrition

In the majority of Paediatric surgical centers, 50-70 % of patients needing parenteral nutrition receive peripheral intravenous nutrition. By using fat emulsions to provide 30-60 % of caloric input, full energy and protein needs can be met through a peripheral vein. The advantages of fat emulsions are that they are isonotic, have a high caloric density, particularly 20 % lipid emulsions, and spare nitrogen as well as dextrose in the presence of amino acids [12].

In infants, this involves insertion of a 21-23 gauge cannula into scalp or a peripheral vein. If there is no facility for preparing a three-in-one solution, then the intravenous tubing from glucose-amino acid solution is connected to the cannula and the tubing from bottle containing lipid emulsion is piggybacked into it. An inline filter is normally used for glucose-amino acid solution, while lipid emulsions are not filtered since their particle size exceeds that of most inline filters. Infusion pumps are desirable to ensure accurate delivery [13].

A major limiting factor for peripheral nutrition is phlebitis. Phlebitis tends to occur more commonly if size of the vein is small, osmolality of the solution is more than 600 mosmols, potassium concentration of the infusate is high, and if antibiotics or sclerosant medications are administered concomitantly. furthermore, to meet the caloric requirements, relatively large amounts of fluid/kg body weight will be necessary. Therefore, peripheral nutrition is not applicable in patients who have a poor venous access or need fluid restriction. Similarly, one should cut the losses and opt for early central parenteral nutrition if the patient is critically ill or likely to need TPN for a long time such as gastroschisis or short bowel syndrome.

Central TPN

Hypertonicity of the TPN solution necessitates its delivery into the superior vena cava. The large diameter and increased volume of blood flow facilitates rapid dilution and peripheral distribution of the nutrients at isotonic concentrations. A fine bore silicone catheter (Vygon, Nutricath S) may be used in neonates, while Broviac or Hickman catheters are suitable fo older infants and children. For short term use polyvinyl or polyurethane catheters may be acceptable.

The superior vena cava may be cannulated by percutaneous puncture of the subclavian, internal or external jugular veins. Percutaneous approach has been reported to be acceptably safe even in neonates weighing less than 1000g [14]. However, it should be stressed that some incidence of malposition, arterial puncture and pneumothorax is not uncommon when percutaneous cannulation is attempted, and junior staff must be closely supervised [1]. Cobb, et. al. have recently documented that in an infant less than one year of age, the internal and external jugular veins follow a straight course into the superior vena cava, while subclavian veins enter the central system at acute angles [15]. Findings of their study suggest that the incidence of catheter malposition will be reduced if internal and external jugular veins are used for percutaneous entry into the central venous system in infants.

Venous cutdown is a more widely used method for central venous cannulation. Most commonly used veins are internal or external jugular vein. However, various veins in the body have been used to gain access to the central system, which include: cephalic, subclavian, cubital, femoral,

long saphenous, azygous, facial middle, thyroid and lumbar veins. If the selected vein is felt to be small, it can be dilated with a venous dilator. Whenever a major vein is used, after obtaining control of the vein, we recommend a small venotom for introducing the catheter and one or two interrupted sutures to close the venotomy around the catheter. If a purse-string suture is used, it tends to occlude the vein and it may not be possible to reuse the vessel. Position of the catheter should always be checked by fluoroscopy, and no fluid be infused through the catheter unless blood can be aspirated freely, even if the catheter is in a satisfactory position on fluoroscopy. Finally, it should be emphasised that tip of the catheter should ideally be in the superior vena cava or atria-caval junction, and, not in the right atrium.

Complications of TPN

In the past, entities such as essential fatty acid deficiency, trace mineral deficiency, vitamin deficiency, and electrolyte disturbances were being listed as complications of parenteral nutrition. However, at present, they could more aptly be described as a result of inadequate TPN or inappropriate monitoring rather than as complications. Discussion in this section will be limited to catheter sepsis and hepatic dysfunction.

Catheter sepsis

Catheter sepsis is a broad term which includes catheter infection, catheter related septicemia and catheter exit site infection. Catheter infection is defined as positive blood culture from the catheter, a negative peripheral blood culture and no other source of infection yielding the same organism. Catheter related septicaemia is present when there is fever with identical blood cultures from both peripheral vein and catheter line blood with no other source possibly yielding the same organism. Catheter exit site infection is present when there is a positive culture from the site or discharge of obvious pus. Gram staining of the catheter removed and semiquantitative or quantitative cultures of the catheter tip are being recommended for more accurate diagnosis of catheter sepsis. Quantitative cultures of peripheral and central blood may also be useful in establishing catheter sepsis.

Initially vancomycin is the antibiotic of choice, if the patient is immunocompromised, an aminoglycoside should be added. Antibiotic therapy should be continued for 7-10 days with modifications depending on results of blood culture. However, the catheter should be removed if there is no satisfactory response to antibiotics within 48 hours, or if the patient is shocked, and in cases of fungal septicaemia. The key to prevention of catheter sepsis is a rigid protocol for catheter maintenance and dressings and keeping line violation for administration of drugs, blood, and blood products to a minimum.

Hepatobiliary complications

This is a spectrum of disorders which includes: slight elevation in serum transaminase, bilirubin, and alkaline phosphatase; cholestatik jaundice; cholelithiasis; tender hepatosplenomegaly: chronic liver diease and hepatic failure. The incidence ranges from 8-40 %. The frequency of fulminant hepatic failure seems to be much higher in children than in adults [16].

TPN induced hepatic dysfunction is multifactorial in origin. Long term TPN, prematurity, abdominal surgery in a neonate, lack of enteral nutrition, presence of sepsis and excess calories, particularly in the form of dextrose appear to be critical factors. On this basis, certain recommendations can be made for reducing the incidence: 1. Utilise the gut whenever possible. 2. Do not over feed, if necessary measure tha energy expenditure using an undirect calorimeter. 3. Use a balanced caloric substrate. 4. Rule out undrained abscesses and other causes of sepsis. 5. Work up alternative causes such as hepatitis [17].

If a patients on TPN develops features of hepatic dsfunction, then reduction in total calories supplied and commencement of some from of enteral nutrition is recommended.

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