Review Article

Essentials of Total Parenteral Nutrition: A review

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Abstract:
The advent of total parenteral nutrition (TPN) in the late 1960s meant that no situation remained in which a patient could not be fed. Unfortunately, total parenteral nutrition was complicated in its early days by serious infective and metabolic side effects that undermined the beneficial effects of nutrient repletion. However, these TPN associated problems were minimized over time with the advancement of science, improvement of infection control measures, invention of suitable equipments, and experience. Now benefits are much greater than drawbacks. In this report we reviewed the literature and documented the indications, composition and preparation, as well as, procedure, and administration of TPN both in children and adults. We also discussed the possible complications of therapy and how to prevent it and manage it when present. We conclude by noting the progress of TPN service in Sudan.

Keywords: artificial feeding, enteral feeding, trace elements, aminoacids

Parenteral nutrition (PN) is feeding a person intravenously, bypassing the gastrointestinal (GI) tract and the usual process of eating, digestion and absorption. The designated person receives nutritional formulas containing salts of minerals, glucose, amino acids, lipids and added vitamins. The mixture is prepared as an aqueous solution with water and given as an IV infusion. Partial parenteral nutrition (PPN) supplies only part of the daily nutritional requirements intravenously, supplementing oral intake. Many hospitalized patients are given dextrose or amino acid solutions by this method. It is called total parenteral nutrition (TPN) when no food is given by other routes. It was described in the medical literature for the first time and tried in the United States in 1968[1]. TPN is indicated in several clinical situations in newborns, children and adults as detailed below. However, parenteral nutrition, total or partial, should not be used routinely in patients with an intact GI tract. In such patients enteral nutrition is the more appropriate option[2]. Compared with enteral nutrition, PN causes more complications, does not preserve GI tract structure and function, and is more expensive.

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Indications:

Parenteral nutrition is indicated to prevent the adverse effects of malnutrition in newborns and children who are unable to obtain adequate nutrients by oral or enteral routes either because of prematurity, necrotizing enterocolitis or other neonatal complications[3,4]. TPN has extended the lives of many children who were born with nonexistent or severely deformed organs, and those who were critically ill[5,6]. Additional indications in childhood are short bowel syndrome, high-output fistula, prolonged ileus, malignant diseases, severe inflammatory bowel disease, malabsorption, and persistent diarrhea[7,8]. However, the decision to initiate PN needs to be made on an individual patient basis, as different patients will have differing abilities to tolerate starvation.

In adults parenteral nutrition is provided when the GI tract is nonfunctional because of an interruption in its continuity or because its absorptive capacity is impaired[9,10]. It has been used also for comatose patients, patients with severe burns, and after surgery[11,12]. Although enteral feeding is usually preferable, and less prone to complications in such cases;

PN speeds recovery and contributes to better prognosis. Short-term TPN may be used if a persons' digestive systems have shut down (for instance by peritonitis or ileus), and they are at a low enough weight to cause concerns about nutrition during an extended hospital stay[13]. Long-term TPN is occasionally used to treat people suffering the extended consequences of an accident, surgery, or digestive disorder [14]. It has also been used in patients with acute pancreatitis and severely sick patients on critical care, as well as in cancer patients [15-17]. PN does not necessarily mean confinement to bed or inpatient care. It can be used on ambulatory basis in some patients [1]. Many patients have survived on total parenteral nutrition for long time (more than 35 years in one report), living fully productive lives.

Composition:

The nutrient solution consists of water and electrolytes; glucose, amino acids, and lipids. Essential vitamins, minerals and trace elements are added or given separately. Previously lipid emulsions were given separately but it is becoming more common for a "three-in-one" solution of glucose, proteins, and lipids to be administered [18]. This is facilitated by the new three plastic bottles set with three-way valve. Adult TPN requires water 30 to 40 ml/kg/day, energy 30 to 60 kcal/kg/day (depending on energy expenditure), amino acids (1.1 to 2.0 g/kg/day (depending on the degree of catabolism), and the daily needs of essential fatty acids, vitamins, and minerals [19]. The composition of TPN in children is different from adults because children need more energy (up to 120 kcal/kg/day) and more aminoacids (up to 3.5 g/kg/day), and their fluid requirements varies with age [20].

The calories in TPN are supplied mainly as carbohydrate. Typically, about 4 to 5 mg/kg/day of dextrose is given. Standard solutions contain up to about 25% dextrose, but the amount and concentration depend on other factors, such as the metabolic requirements of the patient and the proportion of caloric needs that are supplied by lipids. Commercially available lipid emulsions are often added to supply essential fatty acids and triglycerides. Usually 20 to 30% of the required calories are supplied as lipids. However, withholding lipids and their calories may help obese patients mobilize endogenous fat stores[21].

Nutrients for Standard TPN

For adults, standard TPN formulation contains 25% aminoacids, 15% dextrose, and 20% Fat Emulsion; in addition to electrolytes, trace elements, vitamins, and additives. Concentrations may have to be increased with decreased rate and volume. The ideal caloric distribution is as follows: 20% as protein, 60% as carbohydrates and 20% as fat [22].

For pediatric patients below the age of 10 years, 3% aminoacids and 20% fat emulsion are used. Dextrose concentration is calculated based on the patient's weight. If the weight is less than 10kg, 7.5% dextrose is used; otherwise the following formula should be applied:

Dextrose percent =4.45+0.27 x Weight.

Dextrose is increased from about 6mg/kg/min over five days to about 12mg/kg/min, as tolerated. Fat is started at 0.5g/kg/day and increased over five days to a maximum of 4g/kg/day, as tolerated [23].

For newborns and pediatric patients below age five years, fat emulsion is started at quarter the amount required to meet complete caloric requirement. This is gradually increased as tolerated, but guided by serum triglycerides, which should not exceed 150 mg/dl [24]. In most hospitals, clinical pharmacists evaluate the patient's individual clinical data, calculate amount and composition needed, and prepare the parenteral nutrition mixtures accordingly [25].

The amount of TPN solution as well as its content varies depending on the patient's age and his medical condition. However, the following points may be taken as general practical guidelines: 1. For renal insufficiency patients not being treated with dialysis and for patients with liver failure: Reduce total protein content, but provide high percentage of essential amino acids [26], 2. For patient with heart or kidney failure: Limit volume and

calculate total fluid intake carefully, 3. For patients with respiratory failure: Most of the calorie requirement to be given as lipid emulsion rather than carbohydrates to minimize carbon dioxide (CO_2) production that occurs during carbohydrate metabolism, and 4. For neonates: Lower dextrose concentrations e.g. 17 to 18% are advisable [6].

Preparation:

Compounding TPN admixtures has significantly developed since the first clinical reports by Dudrick and colleagues from the University of Pennsylvania approximately 40 years ago[1]. Today, the responsibility for the compounding of safe parenteral nutrition admixtures for patients incapable of oral or enteral nutrition primarily rests with the pharmacy department [27]. Although others may influence the desirable components to be contained therein, no one is more qualified to deal with the physicochemical issues and aseptic technique compounding requirements than a registered pharmacist. In fact, the United States Pharmacopeia (USP), the official drug compendium in the US since 1906, has published chapter 797 entitled "Pharmaceutical Compounding-Sterile Preparations", enforceable by the FDA, and makes clear the role of the pharmacist in the compounding of safe parenteral admixtures. Ultimately, after careful pharmaceutical review of the final formulation, the composition of the final admixture for infusion will be determined based on the ability to safely compound the prescribed additives in the desired quantities of a specified volume of sterile fluid. This is usually done in a dedicated place in the hospital pharmacy, the TPN unit, where aspetic conditions are maintained. A registered nurse, the hospital's infection control officer, and a microbiologist may be part of the TPN team; and frequent auditing is needed to ensure sterile solutions and standard procedures. There will always be instances, where, for example the patient's needs cannot be safely met through the TPN admixture, primarily because of stability, compatibility and/or sterility issues [28]. When this occurs, suitable alternative methods of delivering the additives in question must be sought so as not to compromise the safety issues of the final TPN infusion. Although there have been many advances in the development of nutritional additives, compounding devices, and containers, significant safety issues continue to arise necessitating further modification of parenteral nutrition protocols. The American society of parenteral and enteral nutrition (ASPEN), through periodic reviews of its published guidelines, such as the 2007 Safe Practices for Parenteral Nutrition Formulations, is in a key position to keep nutrition support clinicians and clinical pharmacists abreast of the central issues affecting the safety of TPN therapy [29].

Procedure:

The preferred method of delivering PN is with a medical infusion pump, which allows accurate calculation of amount of fluid and rate of infusion. A sterile bag of nutrient solution with the compounded admixture according to the requirement of the patient is provided. Bags with different sizes are available (from 500 ml to 4 liters). The pump infuses a small amount (0.1 to 10 ml/hr) continuously in order to keep the vein open. Feeding schedules vary, but one common regimen ramps up the nutrition over one hour, levels off the rate for a few hours, and then ramps it down over a final hour, in order to simulate a normal metabolic response resembling meal time. This should be done over twelve to twenty-four hours rather than intermittently during the day [1].

Chronic PN is performed through a central intravenous catheter, usually through the subclavian or jugular vein with the tip of the catheter at the superior vena cava without entering the right atrium. Another common practice is to use a PICC line, which originates in the arm, and extends to one of the central veins, such as the subclavian with the tip of the catheter in the superior vena cava. In newborns, sometimes the umbilical vein is used.

Outpatient TPN practices are still being refined but have been used for years. Battery-powered ambulatory infusion pumps can be

used with chronic TPN patients. Usually the pump and a small (100 ml) bag of nutrient (to keep the vein open) are carried in a small bag around the waist or on the shoulder. Patients can receive the majority of their infusions while they sleep and instill heparin in their catheters when they are done to simulate a more "normal" life style off the pump. Aside from their dependence on a pump, chronic TPN patients can live quite normal lives.

TPN administration:

Because the central venous catheter needs to remain in place for a long time, strict sterile technique must be used during insertion and maintenance. The TPN line should not be used for any other purpose. External tubing should be changed every 24 hours with the first bag of the day. In-line filters have not been shown to decrease complications. Dressings should be kept sterile and are usually changed every 48 hours using strict sterile techniques. If TPN is given outside the hospital, patients must be taught to recognize symptoms of infection, and qualified home nursing must be arranged.

The PN solution is started slowly at 50% of the calculated requirements, using 5% dextrose to make up the balance of fluid requirements. Energy and nitrogen should be given simultaneously. The amount of regular insulin given (added directly to the TPN solution) depends on the plasma glucose level; if the level is normal and the final solution contains 25% dextrose, the usual starting dose is 5 to 10 units of regular insulin per liter of TPN fluid.

Monitoring:

Patients on TPN need careful monitoring and progress should be followed on a flowchart. An interdisciplinary nutrition team, if available, should monitor such patients. Weight, CBC, electrolytes, and BUN should be measured and recorded daily for inpatients. Plasma glucose concentration should be measured every 6 hours until both the patients and the blood glucose levels become stable. Fluid intake and output should be monitored continuously. When patients become stable, blood tests can be done much less often [10]. Complete liver function tests should be done weekly. Plasma proteins (e.g., serum albumin, transthyretin and retinol-binding protein), prothrombin time, plasma and urine osmolality, as well as calcium, magnesium and phosphate should be measured twice per week. Changes in transthyretin and retinol-binding protein reflect overall clinical status rather than nutritional status alone. If possible, blood tests should not be done during glucose infusion. Full nutritional assessment (physically and biochemically) should be repeated at two-week intervals. For patients with central venous lines vigilant observation for symptoms and signs of infection is needed and blood cultures done as appropriate [30].

TPN Support during Bone Marrow Transplantation

Haematopoietic stem cell transplantation (HSCT) is a sophisticated procedure used in the treatment of solid tumours, haematological diseases and autoimmune disorders. All patients undergoing HSCT require intensive chemotherapy and radiation as part of procedure protocol. The majority of those patients suffer from severe mucositis in the oral cavity and oesophagus, and enteritis due to cytotoxic therapy and immune dysregulation, resulting in prolonged decreased oral intake, nausea, vomiting and diarrhea. In addition, cytotoxic drugs enhance catabolism and produced negative nitrogen balance and a greater loss of lean body mass than body weight or body fat mass. The combined adverse effects lead to malnutrition. While total parenteral nutrition is often given to patients in order to maintain their nutritional status during the peri or post transplant period, there is conflicting evidence to support its routine use. The reasons for this controversy may reside in the heterogeneity of the patients studied and of the study designs. Few prospective randomized studies have reported increased survival and decreased relapse in HSCT patients who received TPN compared to control subjects[31,33]. These results suggest that among patients receiving bone marrow transplants,

those who cannot eat for a prolonged period, particularly if they are severely malnourished, may benefit from TPN. However, some other prospective randomized studies showed no difference in survival between TPN and enteral nutrition support in bone marrow transplant recipients[34,35]. We evaluated the small number of prospective randomized and nonrandomized controlled trials that assessed important clinical outcomes such as time to engraftment, rates of infection, overall survival and length of hospitalization. We believe that the data do not support the routine use of parenteral nutrition as first-line therapy but should be reserved for those patients who are unable to tolerate enteral feedings. We also believe that glutamine supplementation cannot be recommended to all HSCT recipients as it has been shown to increase morbidity and mortality rates in autologous transplant patients. Further investigations that test accurate monitoring assessments and incorporate specific substrates such as lipids with parenteral and enteral nutrition are warranted. Novel therapies such as recombinant human keratinocyte growth factor and glucagon-like peptide show future promise in modulating the severity and duration of mucositis, minimizing further the need for TPN.

Complications

TPN complications are fairly common and it is either related to catheter insertion, catheter infection or metabolic side effects. Catheter insertion complications include pneumothorax, accidental arterial puncture, hemorrhage and surgical emphysema [36]. The complication rate at the time of insertion should be less than 5% in the experienced hands.

Infections: The most common complication of TPN however, is bacterial infection [37-38]. The indwelling central venous catheter is associated with genuine risk of infection as long as it is in place, which is increased by manipulation and frequent handling. Catheter-related infections may be minimized by appropriate choice of catheter size and strictly aspetic insertion technique [39,40]. In patients with frequent bacterial infections, fungal infections can also occur especially in patients with compromised immunity. Even when the effect of the catheter is accounted for, patients receiving TPN still have a higher rate of infectious complications than the general population. This may be related to contamination of the infused solutions and hyperglycemia, as well as to the underlying illness [41,42].

Glucose abnormalities: Fluctuations in blood glucose concentration during TPN are common. Hyperglycemia can be avoided by close and frequent monitoring of plasma glucose concentration, adjustment of the insulin dose in the TPN solution, and giving subcutaneous insulin as needed. Hypoglycemia can be precipitated by sudden stopping of the constantly running concentrated dextrose infusions. Treatment depends on the degree of hypoglycemia. Short-term hypoglycemia may be reversed with small amount of 50% dextrose given as IV bolus. More prolonged hypoglycemia may require glucagon injection and infusion of 10% dextrose for 24 hours before resuming TPN via the central venous catheter.

The re-feeding syndrome: This is a potentially fatal complication of the nutritional management of severely malnourished patients[43]. The syndrome almost always develops during the early stages of refeeding. It can be associated with a severe derangement in electrolyte and fluid balance (hypokalemia, hypophosphatemia and hypomagnesemia), and result in significant morbidity and mortality. It is most often reported in adults receiving total parenteral nutrition (TPN), although refeeding with enteral feeds can also precipitate this syndrome.

Hepatic complications: These include hyperammonemia, painful hepatomegaly, and liver dysfunction. Most of these complications relate to the constituents of the TPN and duration of therapy. Excessive carbohydrate administration may contribute to hepatic steatosis, while excess aminoacids are associated with hyperammonemia. Painful hepatomegaly suggests fat accumulation. Reducing carbohydrate is beneficial as excess

glucose is stored as glycogen and fat in the liver under the anabolic effect of insulin. Hyperammonemia can develop in infants, causing lethargy, twitching, and generalized seizures. Arginine supplementation at a dose of 1.0 mmol/kg/day can correct this by enhancing the transformation of ammonia into urea through the alternate pathway of the urea cycle. If infants develop any hepatic complication, limiting amino acids to 1.0 g/kg/day may be necessary. Liver involvement as evidenced by increased transaminases, bilirubin, and alkaline phosphatase can be transient or progressive. The transient type commonly occurs when TPN is started and may result from excess amino acids. Liver enzymes usually return to normal levels with adjustment of aminoacids concentration. However, delayed or persistent elevations of liver enzymes have been observed in some patients without ill effects.

Hepatic dysfunction, which manifests initially as cholestasis, appears to be more common in children. The incidence is highest in premature infants (50%) and in children with a surgical abdomen or peritonitis (25%). The severity of hepatic dysfunction may range from mild elevations in transaminases and bilirubin to frank hepatic failure. Clearly, the duration of TPN is a major factor. Uncomplicated TPN-related cholestasis usually resolves within 1 to 4 months after the cessation of TPN and the institution of enteral nutrition. TPN associated liver disease is usually a relatively minor problem in the acute management of critically ill infants and children, but can be an issue with long term patients. TPN increases the risk of acute cholecystitis due to completely idle gastrointestinal tract, which may result in bile stasis in the gallbladder. The use of cholecystokinin to improve bile flow may offer some benefit prior to the development of end-stage liver disease. A recent small-scale prospective study at Children's Hospital Boston on the cause of liver failure suggests it may be due to a large difference in omega-6 to omega-3 ratio. When treated with Omegaven, a new different solution of fatty acid emulsion, two patients were able to recover and their livers return to normal status.

Adults receiving TPN can have periportal fat infiltration, canalicular plugging, and centrilobular cholestasis. Elevated gamma-glutamyltransferase (GGT), alkaline phosphatase, and hyperbilirubinemia may reflect cholestasis, and less commonly cholelithiasis or cholecystitis. Progressive hepatic destruction and subsequent fibrosis occasionally develops. The pathogenesis of this complication is not completely understood, but cholestasis and inflammation are contributory factors [44-47]. Some studies found that giving parenteral fish oil or intravenous cholecystokinin reverse the liver dysfunction markers [48-49]. However, reducing the amount of protein is the usual recommendation in this complication.

Abnormalities of serum electrolytes and minerals: Electrolytes and acid-base balance are usually maintained during TPN therapy; however electrolyte imbalance is seen occasionally. It should be corrected by modifying subsequent infusions or, if correction is urgently required, by beginning appropriate peripheral vein infusions. Vitamin and mineral deficiencies are rare when solutions are given correctly. Elevated BUN may reflect dehydration, which can be corrected by giving free water as 5% dextrose via a peripheral vein. Volume overload, as suggested by more than 1 kg/day weight gain, may occur when patients have high daily energy requirements and thus require large fluid volumes[50].

Metabolic bone disease: Bone demineralization problems (osteoporosis or osteomalacia), develops in some patients given TPN for more than 3 months. The mechanism is unknown. Advanced disease can cause severe peri-articular, lower-extremity, and back pain. Temporarily or permanently stopping TPN is the only known treatment [51].

Adverse reactions to lipid emulsions: These include dyspnea, cutaneous allergic reactions, nausea, headache, back pain, sweating, and dizziness[52]. It is uncommon, but has been

reported in the course of PN, particularly if lipids are given at a rate providing more than 1.0 kcal/ kg/h. Temporary hyperlipidemia may occur, particularly in patients with kidney or liver failure, but no treatment is usually required. Delayed adverse reactions to infusion of lipid emulsions include hepatomegaly, mild elevation of liver enzymes, splenomegaly, thrombocytopenia, and leukopenia. In premature infants it can cause respiratory distress syndrome, and pulmonary function abnormalities. Temporarily or permanently slowing or stopping of lipid emulsion infusion may prevent or minimize these adverse reactions. Two related complications of TPN are venous thrombosis and priapism, but the later is rarely seen[53]. Fat infusion during TPN is assumed to contribute to bot.
Discontinuation of lipid emulsion and anti-thrombotic therapy may be needed.

TPN in Sudan

TPN services have been introduced in Sudan in the 1980 in Soba University hospital and some other hospitals thereafter. However, it was mainly used for surgical patients and was in the form of ready to infuse aminoacid solutions. Ibn Seena hospital in Khartoum was the first to establish a unit, where TPN is prepared and different components mixed according to patient's requirement under completely aspetic conditions. TPN therapy was not available for newborns and children until recently. Gaffar Ibn Ouf Children Teaching Hospital in Khartoum is the first pediatric hospital to offer this kind of therapy in Sudan. Patients in the neonatal and the gastroenterology units of the hospital are the usual customers. The pharmacy personnel of GIAH have the expertise, the will and the resources to provide TPN mixtures to the in-patients of the hospital and the needy children in other pediatric hospitals in Khartoum. Although the component solutions of TPN are expensive, it is given free of charge to all the babies and children who need it as per hospital policy of free health services including diagnostic and therapeutic measures to all patients. This noble goal is achieved through generous governmental and charity funds.

Conclusion

Total Parenteral Nutrition is important mean of support for critically ill babies and children and for those with GI problems. It is available and affordable and life-saving. The pharmacy staff of Gaffar Ibn Ouf Children Teaching Hospital is willing to give advice and train concerned staff from other hospitals on preparation and administration of TPN. We encourage doctors caring for children to consider TPN as part of their options.

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