Clinical review of total parenteral nutrition use among pediatric: Critics and outcomes

Yelly Oktavia Sari1,2*, Mohd Baidi Bahari3 and Baharudin Ibrahim2
1, Faculty of Pharmacy, Andalas University, Padang 25163, Indonesia
2, Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia (USM)
3, Faculty of Pharmacy, Aimst University Kedah

Abstract

The introduction of total parenteral nutrition (TPN) as an alternative nutrition provided a life saving solution to children with chronic bowel obstructions, fistulas, loss of mucosal body surfaces, short bowel syndrome, and other clinical problems that precluded enteral diet by mouth or tube feeding for long periods of time. Intravenous administration of TPN became an essential fluid to meet nutritional needs and to avoid progressive starvation-induced malnutrition, which changed the outcome of patients from dying. As a result, the prognosis for patients with SBS has changed dramatically and the management with the expected survival for infants with congenital gastrointestinal anomalies and gut failure has improved significantly. However, its use has been shown to associate with an increased incidence of infection. Routine laboratory monitoring may include serum electrolytes, glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, magnesium, albumin, pre-albumin, complete blood count with differential, and iron indices as well as assessment of acid-base status. Routine monitoring of laboratory values is not indicated for medically stable pediatric patients receiving EN at advised levels and achieving adequate growth. There are 2 fatty acids in humans that must be supplied via the diet primarily from plants. They are linoleic and α-linolenic acid and are known as essential fatty acids (EFAs). Patients receiving EN and PN must be adequately supplemented with both EFAs because their oral intake may be minimal. If inadequate amounts are provided, an essential fatty acid deficiency (EFAD) may eventually occur.

Key-Words: TPN, Pediatrics, Clinical care, Parenteral nutrition

Introduction

In the late 1960’s, the introduction of total parenteral nutrition (TPN) as an alternative nutrition provided a life saving solution to children with chronic bowel obstructions, fistulas, loss of mucosal body surfaces, short bowel syndrome, and other clinical problems that precluded enteral diet by mouth or tube feeding for long periods of time. Intravenous administration of TPN became an essential fluid to meet nutritional needs and to avoid progressive starvation-induced malnutrition, which changed the outcome of patients from dying. Since then, TPN has been a gold standard practice in treatment and a panacea for infants and children who are unable to eat or to absorb enteral provided nutrients. As a result, the prognosis for patients with SBS has changed dramatically and the management with the expected survival for infants with congenital gastrointestinal anomalies and gut failure have improved significantly.

* Corresponding Author
Email: yelly.sari@gmail.com

However, its use has been shown to associate with an increased incidence of infection. A number of independent experimental studies have been carried out shown that intravenous TPN negatively influences gut barrier functions and mucosal immunity while withholding nutrients by mouth or enteral tube feeding, after the resection of small intestine. These studies demonstrated that TPN is associated with: 1) increases in intestinal permeability, bacterial overgrowth, and bacterial translocation, 2) rapid changes in gut-associated lymphoid tissue (GALT) T cells, B cell, and secretory immunoglobulin A (S-IgA) levels, 3) impairment in IgA-mediated mucosal immunity defenses in the respiratory tract, 4) impairment in neutrophil function, 5) alteration in gastrointestinal (GI) architecture or mucosal atrophy. This paper presents a descriptive systematic review of published research articles on the effects of the long-term TPN on gut mucosal immunity in children with SBS; specifically, it addresses whether TPN: 1)
promotes bacterial translocation, 2) impairs intestinal mucosal immunity by decreasing S-IgA levels, 3) inhibits neutrophil and cytokine functions in blood, 4) promotes atrophy of the mucosal villi, 5) hyperglycemia, and 6) causes death. It is hoped that these findings will expand the knowledge of pediatric nurses, and have an impact on clinical practice by being included in the pediatric parenteral nutritional guidelines. Since the review of literature did not reveal any systematic reviews of TPN and mucosal immunity on children with SBS, the aim of this descriptive systematic review of individually published scientific studies is to impart a better understanding of the effects of TPN on gut mucosal defense and barrier function. Short bowel syndrome, one of the major indications for diagnostic categories using long-term TPN, is a clinically complex disorder resulting from multiple alterations of normal intestinal anatomy and physiology and producing a variety of nutritional, infectious, and metabolic complications because of impairment caused by vascular disease, intestinal malformations or involvement of other organs such as liver, kidney etc. However, a small number of children have a massive pruritus secondary to marked elevations in the concentrations of biliary acids in the blood. Initially, no intestinal and colonic loops. All children with congenital MVID urgently require total parenteral nutrition (TPN), which often causes rapidly evolving cholestatis and liver disease. A detailed multicenter analysis of 23 patients with MVID allowed two different forms and presentation of MVID to be distinguished on a clinical and morphological basis: congenital early-onset MVID (starting within the first three days of life), and late-onset MVID (with first symptoms appearing after two or three months of life).

**Outcome**

MVID is a constitutive intestinal epithelial cell disease that causes an irreversible diarrheal disorder leading to permanent and definitive intestinal failure. Children with MVID are dependent on exclusive parenteral nutrition throughout their lives. Oral alimentation and appropriate oral caloric intake are impossible. There is no hope for improvement with age. A large number of patients do not survive the first three years of life as a result of infectious complications or rapid evolution, and renal complication. In contrast to children with early-onset MVID, the diarrhea is often less severe in children with the late-onset form of the disease. With age, children...
with late-onset MVID can acquire partial intestinal autonomy, resulting in a reduction of the number of perfusions of parenteral nutrition to one or two a week. Beyhan Duran et al identified five themes: 1) sepsis, 2) impaired immune functions: *In vitro* studies, 3) mortality, 4) villous atrophy, 5) duration of dependency on TPN after bowel resection.

### 1. Sepsis

Six of the 13 trials reported bacterial overgrowth, sepsis, or septicemia. In the first study, investigators reported that two children died from gram-positive central venous catheter infections. In the second study, researchers compared a total of 49 neonates with 7 SBS who were on TPN and 42 weaned children. It was ascertained that the occurrence of bacterial overgrowth was related to small bowel length. Eleven TPN weaned subjects who had bacterial overgrowth had a mean bowel length of 54 cm as compared to 105 cm in those without bacterial growth. In Pierro and colleagues’ study, 41 children whose surveillance cultures developed abnormal carriage. These investigators stated that infants receiving TPN are at a very low risk of developing sepsis and septicemia as long as their surveillance cultures reveal normal flora only. Conversely, the presence of abnormal PPM in the throat and/or the gut increases the risk of sepsis and septicemia to about 25% of the population at risk. They have also stated that the sicker and more physiologically stressed infants would not regain normal gut function as fast as neonates who were doing clinically better. In the third study, the purpose of the investigation was to demonstrate an association between microorganisms that were carried in the digestive tract and present in the blood of infants with sepsis who were receiving TPN. Sepsis occurred in 15 patients (43 episodes) and 10 patients experienced septicemia (24 episodes). Six infants had 15 episodes of bacterial translocation due to *E. coli*, *Klebsiella*, *Candida* species and enterococci. Eight patients had nine episodes of septicemia caused by coagulase-negative staphylococci. The researchers concluded that there was an association between septicemia and elevated serum bilirubin level, indicating TPN related cholestasis. Dahlstrom investigated a total of 29 children, most of whom had SBS and had been on TPN for 2 years. Children receiving TPN for an average of 2 years developed low biochemistry levels. The children were divided into two groups. The children in group I were estimated to have absorbed less than 5% of their daily caloric intake from the intestinal tract, while intake in the children in group II was 30-70%. Based on previous animal studies, the investigator predicted that the low lymphocyte count was related to extensive bowel resection, (the average bowel length of group I was <25 cm). Eleven of these children eventually died from TPN related sepsis, septicemia, central line infections, or cholestatic liver diseases.

### 2. Impaired immune functions: *in vitro* studies

In three *in vitro* control studies, investigators elucidated that long-term TPN in infants suppresses specific mechanisms of immune functions. In the first study, Okada and colleagues (1999) investigated the effects of TPN solution on neutrophil phagocytosis and wholeblood cytokine production in response to coagulase-negative staphylococci in an *in vitro* challenge in five enterally fed infants (age<6 months) and 6 healthy adults. They found that in infants, after 2 hours of incubation with a physiological dose of TPN (1 µ of TPN in 1 ml of blood) there was a significant decrease (P < 0.05) in tumor necrosis factor alpha (TNF-α) production. The other two *in vitro* controlled-clinical trials focused on the cellular mechanism of neutrophil dysfunction, and the whole blood bactericidal activity against coagulase negative staphylococci in the infants receiving TPN. These investigators used an *in vitro*-controlled whole blood model to measure the host bactericidal activity against coagulase-negative staphylococci. When researchers added coagulase-negative staphylococci to whole blood drawn from control patients receiving enteral feeding, the median killing of coagulase-negative staphylococci was 65%. In contrast, blood from infants receiving long-term TPN failed to kill this organism as effectively. Infants on long-term TPN had the lowest levels of both whole blood and intracellular killing of coagulase-negative staphylococci due to a defect in neutrophil function. These investigators reported that there was a negative linear correlation between the duration of TPN in days and killing of coagulase-negative staphylococci (r = 0.80, P < 0.05). For every additional week of TPN, there was a 7% reduction in killing of coagulase-negative staphylococci. These investigators also noted that there was a significant positive correlation between neutrophil count and killing of coagulase-negative staphylococci (r = 0.80, P = 0.001).

### 3. Mortality

A total of 34 TPN complicated deaths were reported in five of the 13 clinical trials. Of these 34 deaths, 7 children died from SBS, 12 from sepsis, respiratory infections, and low immune deficiency, and other 15 from liver failure.
4. Duration of dependency on TPN after bowel resection

There were only three studies, retrospective and case study that showed the dependency on TPN in infants who had undergone resection of the small intestine. As reported in these studies, there were only 17 children who were totally dependent on TPN, and nine of them died while on TPN. In one of these studies, investigators also noticed that no child successfully discontinued TPN after 36 months of age. They concluded that children dependent on TPN at or more than 36 months of age are permanently dependent on TPN. Andorsky and his coworkers also emphasized that residual bowel length was highly correlated with duration of TPN. Their conclusion was that remaining functional small bowel length was an independent predictor of successful weaning. Although most children had difficulty being weaned from TPN in studies such as Andorsky and colleagues', Bines and her co-workers were able to wean all four children from TPN within 15 months of initiation of a study formula. They used an amino acid-based complete infant formula (Neocate, SHS Inc, Rockville, MD, USA) as enteral feeding. Small bowel length of these children was documented between 40 cm to 80 cm with no ileocecal, and in only one child had 13 cm with ileocecal present. All patients had repeated esophagastroduodenoscopy and colonoscopy or jejunoscopy with findings of mild, nonspecific neutrophilic inflammation involving areas from biopsy specimens from upper and lower intestinal tract. In addition, two other studies used enteral formulas while children were on TPN. Andorsky and colleagues fed the patients with continuous breast milk or protein hydrolysate formula. Of the 30 patients in the study, 20 were weaned from TPN. Based on their report, median residual bowel length was 61 cm, and ileocecal valve was preserved in 57% of the patients. There was a significant high correlation between use of breast milk and shorter the duration of TPN. Infants who received breast milk were weaned from TPN in 290 days versus 720 days in non-breast-fed infants.

5. Villous atrophy

In two separate clinical trials, researchers examined whether the effects of TPN on the intestines of children are similar to those reported in animals. In the Rosi and colleagues' study, a total of 32 children (ages 9 months to 19 years) were involved. Based on the biopsy results, the investigators reported that 3 of the 4 patients receiving long-term parenteral nutrition for short-bowel syndrome (TPN >7 months) had mild villous atrophy. Biopsies from 3 patients in the inflammatory bowel disease (IBD) group (TPN = 1 month) did not exhibit atrophy. Bines and colleagues also reported similar results; in their study only one of four children (bowel length, 40 cm) had partial villous atrophy of the small intestinal mucosa.

Monitoring Laboratory Values in Pediatrics TPN

Routine laboratory monitoring may include serum electrolytes, glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, magnesium, albumin, pre-albumin, complete blood count with differential, and iron indices as well as assessment of acid-base status. Routine monitoring of laboratory values is not indicated for medically stable pediatric patients receiving EN at advised levels and achieving adequate growth. Serum zinc may need to be monitored when fat malabsorption is present. Physical assessment including clinical signs of nutrient excess. Prealbumin is commonly used to monitor protein status due to its shorter half-life of 2 to 3 days in comparison to albumin. However; there are other factors that can influence prealbumin levels such as inflammatory states, end-stage liver disease, untreated thyroid disease, renal disease, and zinc deficiency. These limitations should be considered when interpreting a patient’s prealbumin level. Monitoring of prealbumin levels can be helpful especially for long-term stable patients. Prealbumin can be monitored on a weekly basis initially and then monthly in stable patients. Changes in triglyceride levels can be influenced by a variety of factors including disease state, organ function, medications, nutrition status, and current nutrient intake. They should be monitored daily when SNS is initially started, followed by a weekly level, and then increased to monthly. Carnitine is often supplemented in the formula of PN patients, particularly neonates and infants due to their inability to synthesize an adequate amount. In addition, premature neonates will also have limited carnitine stores that are needed for long-chain fatty acid transport. A deficient patient may present with increased triglyceride levels, hyperbilirubinemia, or decreased weight gain along with a multitude of other clinical symptoms. Carnitine dose of 10 to 20 mg/kg/d is recommended for IV or oral supplementation and should be initiated in any patient receiving PN for > 7 days. Currently, a carnitine profile including ester/free ratio, should be monitored every 3 to 6 months if the patient is being supplemented. A yearly carnitine profile is sufficient for patients not receiving supplementation.
There are 2 fatty acids in humans that must be supplied via the diet primarily from plants. They are linoleic and α-linolenic acid and are known as essential fatty acids (EFAs)\(^6\). Patients receiving EN and PN must be adequately supplemented with both EFAs because their oral intake may be minimal. If inadequate amounts are provided, an essential fatty acid deficiency (EFAD) may eventually occur. If lipid-free PN is provided for a significant amount of time or there is clinical manifestation of an EFAD, it is possible to order an EFA profile. The resulting triene:tetraene ratio can determine if an EFAD exists\(^6\).\(^5\).

Table 1: Contents of TPN and monitoring plans

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>INITIAL</th>
<th>FOLLOW–UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMP</td>
<td>Daily</td>
<td>Included in CMP</td>
</tr>
<tr>
<td>CMP</td>
<td>Weekly</td>
<td>Every 1 to 4</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Daily</td>
<td>Every 1 to 4</td>
</tr>
<tr>
<td>Phosphorous</td>
<td>Weekly</td>
<td>Every 1 to 4</td>
</tr>
<tr>
<td>Prealbumin</td>
<td>Daily</td>
<td>Monthly</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Weekly</td>
<td>Monthly</td>
</tr>
<tr>
<td>PT/INR</td>
<td>Weekly</td>
<td>Every 1 to 4</td>
</tr>
<tr>
<td>CBC differential/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>platelets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>Baseline if indicated</td>
<td>Every 1 to 4 weeks</td>
</tr>
</tbody>
</table>

Table 2: Nutritional contents and monitoring issues

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>INITIAL</th>
<th>FOLLOW–UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Studies</td>
<td>3 mo</td>
<td>Every 3–6 mo</td>
</tr>
<tr>
<td>Zinc</td>
<td>3 mo</td>
<td>Every 3–6 mo</td>
</tr>
<tr>
<td>Selenium</td>
<td>3 mo</td>
<td>Every 3–6 mo</td>
</tr>
<tr>
<td>Manganese</td>
<td>3 mo</td>
<td>Every 3–6 mo</td>
</tr>
<tr>
<td>Copper</td>
<td>3 mo</td>
<td>Every 3–6 mo</td>
</tr>
<tr>
<td>Chromium</td>
<td>3 mo</td>
<td>Every 3–6 mo</td>
</tr>
<tr>
<td>Vitamins A, D,</td>
<td>6 mo</td>
<td>Every 12 mo</td>
</tr>
<tr>
<td>and E</td>
<td>6 mo</td>
<td>Every 12 mo</td>
</tr>
<tr>
<td>Vitamin B12 and</td>
<td>3 mo</td>
<td>Every 3–12 mo</td>
</tr>
<tr>
<td>Folate</td>
<td>Baseline if indicated</td>
<td>Every 12 mo</td>
</tr>
<tr>
<td>Carnitine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug Compatibilities in Pediatrics TPN

Drugs Compatible with Parenteral Nutrition\(^*\)

The tables below list the drugs that are compatible with parenteral nutrition and those that are not. For the most recent information, see the current SickKids Formulary of Drugs\(^6\).

**Table 3: List of drugs compatible with Parenteral Nutritions**

<table>
<thead>
<tr>
<th>Ampicillin</th>
<th>Fluconazole</th>
<th>Metoclopramide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>Furosemide</td>
<td>Morphine</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Gentamicin</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Heparin</td>
<td>Penicillin G</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Insulin</td>
<td>Piperacillin</td>
</tr>
<tr>
<td>Clindamyci n</td>
<td>Isoproterenol</td>
<td>Ranimidine</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>Lidocaine</td>
<td>Tazocin®</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Meperidine</td>
<td>Tobramycin</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Methylprednisol e</td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

**Table 4: List of drug not compatible with Parenteral Nutritions**

| Acetazolamide | Cisplatinum | Mannitol |
| Acyclovir     | Cyclosporine| Metronidazole|
| Amphotericin  | Deferoxamine| Pantoprazole |
| Antithymocyte | Doxorubicin | Phenyltoin  |
| Globulin      | Etoposide   | Sodium     |
| (ATGAM)       | Ganciclovir | Bicarbonate |
|              |             | Teniposide |

\(^*\)For compatibility information on any drugs not listed, contact the pharmacy department.

Drugs Incompatible with Parenteral Nutrition

The following drugs are incompatible with PN and must not be given concurrently with a PN solution under any circumstances. These drugs may be administered through a Y-connection, provided that the PN solution is stopped and the line clamped immediately above the Y, then adequately flushed\(^6\).

**Table 4: List of drug not compatible with Parenteral Nutritions**

| Acetazolamide | Cisplatinum | Mannitol |
| Acyclovir     | Cyclosporine| Metronidazole|
| Amphotericin  | Deferoxamine| Pantoprazole |
| Antithymocyte | Doxorubicin | Phenyltoin  |
| Globulin      | Etoposide   | Sodium     |
| (ATGAM)       | Ganciclovir | Bicarbonate |

• Drug compatibilities with PN solutions can never be guaranteed\(^6\).
• If there is a separate IV site or catheter lumen available, use it for drug administration\(^6\).
• If the PN is turned off for scheduled drug administration, cycle the total PN prescription over the number of remaining hours\(^2\).\(^4\).

For drugs not listed above, the following steps are taken\(^6\):

1. The pharmacist can discuss with the nurse, physician or dietitian the possibility of finding a separate IV site or turning off the PN to allow drug administration. If a patient’s condition allows, new rates can be suggested that would give the required PN volume over the number of hours available.
2. If this is not possible, the pharmacist can discuss the situation with the prescribing healthcare professional. The pharmacist relays the information available on the drug and the individual patient is assessed.
3. The physician makes the decision to run (or not to run) a drug simultaneously with PN.
4. The physician documents the decision as a physician’s order, e.g., Drug X may be run concurrently with PN.

In all cases where drugs are infused concurrently with PN solutions, the IV lines should be carefully monitored for signs of incompatibility.

Discussion

Systematic reviews focus on empirical studies and seek to summarize past research by drawing overall conclusions from many separate investigations that address related or identical hypotheses. The purpose of this descriptive systematic review was to assess the literature documenting whether TPN negatively influences gut barrier function and is associated with increases in intestinal bacterial overgrowth, bacterial translocation, decreases in mucosal permeability, decreases in S-IgA levels, and changes in mucosal architecture in infants and children after small bowel resection. Thirteen clinical trials in children from 1990 to 2001 examined the effects of TPN on infection, mortality, impaired intracellular immune functions, villous atrophy, and long-term TPN dependency. These studies were conducted in four countries from various disciplines; they ranged in size from 4 to 94 children, and age from approximately 4 months to 17 years old, with the majority of children spending time in hospital. Numerous experimental studies suggest that long-term TPN has harmful effect. Evidence in experimental studies about TPN’s effects on mucosal immunity and villous atrophy is very convincing, however, findings in human subjects were inconsistent. Although animal models provide us wealth of evidence and continue to offer valuable information to apply to clinical conditions, Rossi and coworkers argue that extrapolating these results to apply to the human model is inappropriate. Their study results showed that infants with SBS on TPN for more than 9 months had only minimal grade villi atrophy. They concluded that humans are more resistant to hypoplastic intestinal changes induced by TPN; and effects in humans seem to require longer periods of TPN. In adults, 203 surgical patients who had at least 10 days of preoperative TPN without enteral nutrients, no significant decrease in villous height or increase in bacterial translocation were noted compared with those on enterally fed controls. Guédon and colleagues performed biopsies in 2 adult patients who underwent long-term TPN for the treatment of a postoperative enterocutaneous fistula, and their results showed changes in villous height and crypt depth after 2 and 3 months of TPN; two months after oral refeeding, the values of morphometric parameters were significantly greater than those observed after TPN and were similar to those controls. Groos and colleagues also conducted a study involving 20 adults to investigate whether TPN causes morphological changes in intestinal mucosa of human adults similar to those observed in animals experiments. They found jejunal mucosal atrophy, and a remodeling of luminal surface architecture with disappearance of cell shedding.

(Beyhan Duran et al) Based on this exhaustive literature review, there is no direct evidence suggesting that TPN promotes bacterial overgrowth, impairs neutrophil functions, inhibits blood’s bactericidal effect, causes villous atrophy, or causes to death in human model. The hypothesis relating negative effects of TPN on gut immunity remains attractive, but unproven. Enteral nutrition is cheaper, but no safer than TPN. Based on the current evidence, TPN seems to be safe and a life saving solution.

References

Review Article


Review Article
CODEN (USA): IJPLCP


51. Groos S, Hunefeld G, Luciano L: Parenteral versus enteral nutrition: morphological changes in human...


