

Research Article

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Correlation of transaminase elevation and mortality in patients on total parenteral nutrition: A hospital-based retrospective study

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Abstract

Background: Total Parenteral Nutrition (TPN) is a life-saving intervention for patients with an inability to tolerate alternative nutrition. However, elevated liver enzymes in patients on TPN are a significant predictor of morbidity and have been associated with increased mortality rates.

Methods: This retrospective study examined electronic records at Henry Ford, Michigan, USA, from January 2014 to January 2024. We retrieved patients who received parenteral nutrition and then included those with elevated transaminases during treatment in the study. Data on indication for TPN, prior history of liver disease, pattern of injury (hepatocellular, cholestatic, or mixed), workup obtained, and mortality was collected.

Results: A total of 111 patients with elevated liver enzymes were included. 63(56.7%) patients had a history of prior liver disease, with the most common indication for TPN being prolonged malnutrition in 41(36.9%) patients.

Mortality occurred in 52(46.8%) patients. Indication for TPN ($p=0.82$) and Duration of TPN therapy ($p=0.516$) did not show statistically significant differences in mortality risk. There was a statistically significant association of Alanine aminotransferase (ALT) with mortality, with $p=0.022$, and Alkaline Phosphatase (ALP) with mortality, with $p=0.034$. A total of 10.1% of patients had cirrhosis and suffered from ascites and line clots without a mortality difference.

Conclusions: Our investigation suggests that people with TPN-associated LFT elevation have high mortality irrespective of duration and indication. Commonly associated markers were ALT and ALP.

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Introduction

Intestinal failure, characterized by insufficient intestinal absorption to sustain life, often necessitates intravenous nutritional supplementation in the form of parenteral nutrition. It may be reversible, as witnessed post-operatively (type 1) or permanent (type 2-3), due to widespread mucosal erosion (inflammatory bowel disease), impaired motility (diabetics), or surgical resection [1-3]. Underlying disease contributes to most of the mortality associated with parenteral nutrition [4,5]. An exception is the development of liver disease, which has a 3%-26% mortality [1,6]. It is referred to as Intestinal Failure-associated Liver Disease (IFALD)/Parenteral Nutrition-Associated Liver Disease (PNALD).

In 1971, Paden et al. [3] first recognized hepatobiliary complications in infants on Total Parenteral Nutrition (TPN). IFALD is a spectrum of diseases that can range from mild liver enzyme abnormalities, cholestasis, and steatosis to eventual fibrosis or cirrhosis [4,5]. The etiology of IFALD is multifactorial and presents with different histological patterns of liver damage [6].

Cholestasis can be explained by a lack of physiologic stimulation. However, it has further been associated with various factors, including inhibition of the Farnesoid-X receptor associated with the use of soy-based TPN and the loss of FGF signaling through interruption of enterohepatic cycling [7]. These molecular changes cause biliary epithelial damage, thereby resulting in metallothionein protein deposition in periportal areas, which hinders biliary excretion, further contributing to cholestasis, and even leading to periportal fibrosis.

Steatosis occurs due to non-physiological delivery of lipid micelles, lipogenesis within the liver due to excess carbohydrate delivery, and the lack of entero-pancreatic endocrine secretion in the absence of diet-related incretin release [8]. This leads to the development of reactive oxygen species, causing inflammation, progressive fibrosis, and ultimately resulting in the rapid onset of decompensated cirrhosis [9,10].

Medical risk factors for IFALD include ultra-short gut with less than 20 cm of remaining small intestine, bacterial or fungal infections, and small intestinal bacterial overgrowth. Nutritional risk factors include excess calories, excess lipids, soybean-based emulsions, and a complete lack of enteral stimulation.

IFALD also presents as a diagnostic challenge. Firstly, abnormal tests in critically ill patients on parenteral nutrition can be related to ischemic liver injury [11]. Secondly, with a lack of enteral stimulation, splanchnic blood flow, and hence portal venous return, decreases, decompressing the portal vein in the cirrhotic subgroup and delaying complications attributed to portal hypertension like encephalopathy and varices.

Recommendations, such as preventing excess calories, a more appropriate ratio of energy from glucose and fat, and early enteral feeding, are important in the prevention [12,13]. Enteral stimulation can promote enterohepatic circulation of bile acids, reducing the risk for hepatobiliary complications seen in long-term PN use [14].

Our study aims to study different patterns of transaminase elevation and determine if a certain kind of elevation has a higher mortality risk. Further retrospective study seeks to illuminate complications in cirrhotic patients receiving TPN. In our study, we look for complications due to decompensation and their contribution to overall mortality.

Methods

Study design and patient recruitment

We present a retrospective study using hospital-based surveillance data from the Henry Ford Health System, 5 hospitals in the network, including Detroit, Jackson, Macomb, Wyandotte, and West Bloomfield in Michigan, USA. We examined medical records on patients requiring total parenteral nutrition from January 2014 to January 2024. The study was approved by the institutional review board.

Data collection

The electronic database was searched for patients requiring TPN in the past 10 years. Around 111 cases were identified that had an elevation in transaminases while receiving the treatment.

Data analysis

Authors extensively reviewed all the cases for time to peak of transaminases, mean elevation, changes in TPN upon transaminase elevation, complications in patients with pre-existing liver disease, and association of transaminase elevation with mortality and morbidity.

Statistical analysis

Descriptive statistics were applied to describe patient characteristics. Categorical variables were analyzed by Pearson's chi-squared test. The significance level was set at 0.05.

Results

Of all 426 patients with TPN use, 111 showed transaminase elevation. 48 (43.2%) were male, and 87 (78.4%) were Caucasian. The most common indications for TPN initiation were prolonged malnutrition in 41 (36.9) patients and short gut syndrome in 39 (35.1) patients. 63 (56.7%) patients had a history of prior liver disease. Mortality occurred in 52 (46.8%) of patients (Table 1).

Table 1: Demographics.

Characteristic	Value
Total patients with TPN	426
Patients with transaminase elevation	111
Male patients	48 (43.2%)
Caucasian patients	87 (78.4%)
Prolonged malnutrition (TPN Indication)	41 (36.9%)
Short Gut syndrome (TPN Indication)	39 (35.1%)
History of liver disease	63 (56.7%)
Mortality	52 (46.8%)

Table 2: Analysis of transaminase elevation with mortality.

Transaminase	Associated mortality (p-value)	Mean time to mortality (transient/permanent) in days
AST	0.42	38.56/301.69
ALT	0.022	63.83/328.1
ALP	0.034	70.8/328.1

Aspartate Aminotransferase (AST) elevation

There was no association between the elevation of AST and mortality, with a p-value of 0.42. The mean time of death from the peak was 38.56 days in the population with transient (<30-day duration) and 301.69 days in the population with persistent elevation (>30 days).

Alanine Aminotransferase (ALT) elevation

There was a statistically significant association of ALT with mortality, with a p-value of 0.022, with a mean time to mortality of 63.83 days in transient and 328.1 days in persistent elevation.

Alkaline Phosphatase (ALP) elevation

There was a statistical association between ALP elevation and mortality, with a p-value of 0.034, with a mean time to mortality of 70.8 days and 328.1 days in the two respective groups.

Bilirubin elevation

There was no association ($p>.05$), and the duration to death was 70.8 days and 190.8 days in the transient and permanent groups.

Association with change in TPN after LFT elevation

Further, people with TPN change had a higher mortality with $p=0.014$, with a mean time to death of 31.79 days in the change group versus 36 days. Most changes in TPN have been associated with ALP and total bilirubin elevation with $p = 0.028$ and 0.036 , respectively.

Sub-analysis of cirrhotic patients:

There was no association between cirrhosis and mortality, $p=0.068$. There was a total of 12 cirrhotic patients. 9/12 cirrhotic patients died, compared to 43/95 non-cirrhotic patients.

Four out of twelve cirrhotic patients had line infections, one had a central line clot, and seven had worsening ascites.

The power of the study was too low to deduce convincing results.

Discussion

Since the use of TPN by Dudrick and colleagues, it has paved the way for nutritional support in patients with intestinal failure [2]. On average, an ideal TPN contains carbohydrates, making 70–85% of nonprotein energy at ≤ 7 g/kg/day, and lipids, making 15–30% of nonprotein energy at <2.5 g/kg/day [15,16]. It, however, is associated with complications such as hepatobiliary, infectious, and metabolic disorders like hyperglycemia and hypertriglyceridemia [15,16]. Our study focuses on the hepatobiliary injury with TPN, more commonly called IFALD.

Patients started on total parenteral nutrition are relatively sicker, making them more prone to higher mortality compared to other patient populations. Nutrition is crucial for overall re-

covery, but it also makes the patients prone to risks, including IFALD. Whether the initial pre-existing insult is responsible for mortality or the complications of TPN is always a matter of interest. This study did not find any correlation between mortality and indication and duration of TPN, with $p=0.82$ and $p=0.516$, respectively.

Common indications for TPN in our study included prolonged malnutrition and short gut syndrome. People with prolonged malnutrition are generally hospitalized, requiring parenteral nutrition due to contraindications to enteral feeding. In contrast, people with short gut are more chronically dependent on TPN, even using it at home due to a relative malabsorptive state. The former are expected to have higher mortality, but the lack of a statistically significant association with mortality indicates more of a TPN/IFALD-associated mortality.

Secondly, the duration of TPN had no statistical significance. This can be partially explained by a dual-fold phenomenon. The patients were split into a less than 30 and a greater than 30-day dosing. Less than 30-day dosing incorporates people who only required it for a few days before recovery and people who passed away sooner due to pre-existing co-morbidities. Now, the prolonged treatment group had short bowel syndrome patients who were using it at home and then hospitalized patients who passed away after a month. A subgroup analysis comparing indications in the two groups separately was warranted.

Further, IFALD can be divided into two types. Firstly, steatosis refers to the accumulation of fat in the liver. This presentation typically occurs within 2 weeks of PN initiation. Pathogenesis is non-physiologic lipids in TPN or hepatic lipogenesis due to the delivery of excessive carbohydrates. Other than macronutrient imbalance, formulations hold a crucial role. Soybean oil-based emulsions contain a high dose of omega-6 fatty acids and large amounts of phytosterol [17,18]. Farnesoid-receptor inhibition by phytosterols impairs biliary synthesis and clearance, producing hepatocellular injury. Omega-6 fatty acids via the nuclear factor-kB pathway activate TNF- α , disrupting hepatobiliary transport [11]. It further enhances peroxidation and decreases antioxidants, mainly tocopherol [11]. Together, they contribute to liver injury, leading to IFALD. Pure fish oil has been shown to reverse IFALD since it contains anti-inflammatory omega-3 fatty acids, which could potentially decrease the risk of IFALD development or provide treatment for those with preexisting IFALD [9,10].

Secondly, cholestasis and gallstones, indicated by high conjugated bilirubin levels. It is often defined biochemically as 1.5 times the upper limit of normal elevation of two out of the following liver tests: gamma-glutamyl transferase or alkaline phosphatase, and/or serum conjugated bilirubin ≥ 2 mg/dL [12,14]. Elevation occurs within 1 to 3 weeks of initiating PN [19,20]. Although changes typically seen in IFALD occur in long-term PN, biochemical signs may occur even after the first week. The lack of enteral stimulation leads to reduced cholecystokinin production, hence impaired bile flow and gallbladder contractility, and consequently, cholestasis, gallbladder hypotony, and gallstone formation [19-22]. Manganese, aluminum, and chromium have been explored in this context. Cholestasis has been observed during manganese-containing PN administration, tied to its excretion via the biliary route [11]. Copper is also eliminated with bile, and since it is only a trace element in PN solutions, it does not have direct hepatotoxic effects; however, in patients who develop cholestasis, copper should be eliminated from the PN formulation due to potential hepatotoxicity.

The results for the study indicate that ALT elevation is more strongly associated with mortality, followed by ALP. Most of the TPN changes were made in association with cholestatic changes and were associated with higher mortality. There was no association with AST or bilirubin, making a clear association between purely hepatocellular versus cholestatic injury unclear. It cannot be extrapolated that mortality is higher in cholestatic injury compared to steatosis or vice versa.

Lastly, our findings suggest that TPN is associated with cirrhosis decompensation, with ascites being the most common complication likely in the setting of volume overload. However, mortality is not significantly associated with pre-existing cirrhosis; rather, cirrhosis had a larger difference between peak value and death. This can indicate that cirrhotic decompensation generally occurs slowly over time, whereas non-cirrhotic patients generally die of liver failure, which has a short course till death.

Limitations

The study has its limitations. The size of the study is extremely small, and the external validity of the data can be questionable. There is no stratification of patients based on MELD or Child-Pugh score. Lastly, whether the mortality was directly associated could not be established. This underscores the need for further research to identify an association between transaminase elevation in IFALD and mortality.

Worsening IFALD requires intestinal transplantation, with it being a major indication in the pediatric population. The majority of patients require a liver graft in addition due to the late stage of presentation. Hence, more data regarding the benefits of only intestinal transplants have been coming up, including reduced wait times [23]. However, once the liver disease has progressed too far, a liver transplant is required.

Conclusion

Our investigation suggests that people with TPN-associated LFT elevation have high mortality irrespective of duration and indication. Commonly associated markers were ALT and ALP. Cirrhotic people do face complications, but they did not show a mortality change.

Due to the potential for rapid development and progression of IFALD, patients should be discussed with an intestinal transplant center at the earliest possible opportunity following an enterectomy that leaves them with an ultrashort bowel.

Further research is required on the effect of intestinal failure and long-term parenteral nutrition on liver disease.

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