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Total Parenteral Nutrition-Associated Cholestasis in Surgical Neonates

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Abstract: Purpose: The aim of this study was to determine the risk factors in the development of total parenteral nutrition associated cholestasis which is a significant clinical problem for pediatric surgeons.

Methods: The medical records of 54 neonates who had received total parenteral nutrition for more than two weeks were reviewed retros pectively. Prematurity, duration of parenteral nutrition, enteral starvation, composition of the parenteral nutrition solution, the number of septic episodes and the presence of jejunostomy were evaluated as risk factors. The results were analyzed by dividing the patients into two groups, based on conjugated plasma bilirubin levels (greater or less than 2 mg/dl) during total parenteral nutrition.

Results: There were significant differences between the two groups with respect to birth weight, gestational age at birth, duration of enteral starvation, the number of septic episodes and the presence of jejunostomy.

Conclusion: The interruption of enterohepatic circulation (by enteral starvation, IV administration of nutrients and the presence of jejunostomy) is one of the most important factors in the development of total parenteral nutrition -associated cholestasis.

Key Words: Total parenteral nutrition, cholestasis, enterohepatic circulation.

Introduction

The major complication of total parenteral nutrition (TPN) in neonates is cholestatic jaundice leading to liver failure. Although enteral feeding in otherwise healthy neonates has almost eliminated total parenteral nutrition-associated cholestasis (TPNAC), it remains a significant clinical problem for the pediatric surgeon who treats neonates with diseases of the gastrointestinal tracts that require prolonged parenteral nutrition. Its pathogenesis is not well known. Abdominal surgery, enteral starvation, number of operations, prematurity, recurrent septicemia from the central venous catheter, and intestinal bacterial overgrowth, duration of parenteral nutrition and composition of TPN solution have been identified as potential factors in the development of TPNAC (1-6).

The aim of this study was to determine the risk factors, including the presence of jejunostomy which interrupts enterohepatic circulation of bile acids.

Materials and Methods

Fifty-four neonates who had received TPN for more than two weeks were included in the study. They were followed up until the TPN was discontinued or until death. The medical records of the 54 neonates were reviewed, and the following data were extracted: birth weight, gestational age at birth, age at beginning of TPN, total duration of TPN, the composition of TPN solutions, duration of enteral starvation, number of septic episodes (defined as positive blood culture in association with one or more of the following symptoms: fever, hypothermia, hypotonia, hypotension, trombocytopenia, elevated neutrophil count), plasma bilirubin levels and the presence of jejunostomy.

The diagnoses were gastroschisis (10), necrotizing enterocolitis (9), intestinal atresia (11), meconium ileus (6), malrotation with midgut volvulus (7), bacterial sepsis (3), and others.

The results were analyzed by dividing the patients into two groups, based on conjugated plasma bilirubin level (greater or less than 2 mg/dl) during TPN. The parameters were compared in each group, using the Mann-Whitney U test or the Yates' corrected chi square test where appropriate.

Since some parameters are linked, the multiple logistic regression test was used to relate TPNAC to possible associated factors.

Results

Cholestatic jaundice had developed in 16 subjects (29.6%). Two subjects who had jejunostomy died of liver failure. Three subjects died of other causes. Eleven subjects were weaned from TPN, and cholestasis resolved after cessation of TPN within three months. The results of the comparison of the two groups are summarized in table 1. Birth weight, gestational age at birth, the duration of TPN, duration of enteral starvation, the number of septic episodes, and the presence of jejunostomy differed significantly between the two groups, while there were no significant differences in the interval between birth and beginning of TPN and the composition of TPN solution.

Multiple regression analysis indicated that the best predicting factors for TPNAC were the presence of jejunostomy ($p<0.001$), gestational age at birth ($p<0.05$), the number of septic episodes ($p<0.05$) and total duration of enteral starvation ($p<0.05$). Interval between birth and beginning of TPN, total duration of TPN and the composition of TPN solution were found to be unimportant predicting factors for TPNAC.

Discussion

Moss et al. (6) demonstrated that biochemical indices of liver function do not necessarily correlate with liver histology. However, our diagnostic criterion for TPNAC is elevation of plasma conjugated bilirubin levels, because of the impossibility of doing the liver biopsy in all neonates who receive TPN.

One of the factors in the development of cholestasis is prematurity. This result is in agreement with previous studies (2, 5), and supports the hypothesis that TPNAC is primarily attributable to immaturity of the neonatal hapatobiliary system (7, 8). Unfortunately, most surgical neonates dependent on long term TPN had low birth weight and low gestational age and TPNAC may be unavoidable.

Several studies have implicated the role of intestinal bacterial overgrowth and septicemia in the development

Table 1. The comparison of cholestatic and noncholestatic neonates

Parameter	Cholestatic (n:16)	Noncholestatic (n:38)
Birth weight (kg)	2.13 (1.2-3.4)	2.41(1.5-2.9)#
Gestational age at birth (wk)	35.9 (28-40)	37.4 (30-40)#
Time between birth and beginning of TPN(day)	3,6 (2-11)	6.1 (2-17) NS
Total duration of TPN (day)	42.4 (18-96)	24.7 (14-56)#
Total duration of enteral starvation (day)	35 (11-52)	21.7 (8-37)#
Composition of TPN solution		
a.a. gr/kg/day	2.81 (2-3.5)	2.79 (2-3.5) NS
lipid gr/kg/day	3.6 (3-4)	3.51 (3-4) NS
carbohydrate gr/kg/day	17.11 (13-21)	15.65 (13-20) NS
No of septic episodes	2.1 (0-7)	0.7 (0-4)#
No of subject with jejunostomy*	6 (37.5%)	0 (0%)#
Maximum conjugated bilirubin mg/dl	7.1 (2.3-15.0)	1.1 (0.3-1.9)

Data are expressed as mean value and ranges, statistical analysis was performed the Mann-Whitney U test and Yates' corrected chi square test (*), # $p<0.05$, NS not significant.

of TPNAC (2, 3, 5, 9). Further supporting this are studies that have shown a decreased incidence of liver disease when metranidazole and gentamycine are administered during TPN (9-12). Bacterial endotoxins (e.g. *E. coli* endotoxin), which decrease Na+ - K+ ATPase activity in the membrane of hepatocytes, may also decrease bile flow (13).

The most widely accepted hypothesis for the explanation of TPNAC is that a lack of fat in the duodenum leads to stasis in the enterohepatic circulation, which then leads to the histological changes seen in the liver in this syndrome. Conjugated hyperbilirubinemia together with elevated serum bile acid levels is part of TPNAC.

The passage of bile salts into the biliary canaliculus is the most important factor promoting bile formation. There is an excellent correlation between bile flow and bile acid secretion. The bile-acid-dependent pump fails if inadequate quantities of bile acids reach the canaliculus or leak from it. Failure of enterohepatic circulation of bile acid may contribute. It is suggested that ursodeoxycholic acid is actively absorbed by the ductular cells and recirculates to the liver for further excretion (13). The restoration of the bile acid pool by administration of ursodeoxycholic acid increases the bile acid secretory rate and bile flow.

The combination of an enteral fast with the IV administration of all nutrients in a young rabbit resulted in bile acid sequestration in an adynamic gallbladder with the interruption of the enterohepatic circulation (14). Apart from enteral starvation and IV administration of nutrients, the presence of jejunostomy interrupts the enterohepatic circulation mostly since the majority of bile acids are actively absorbed in the terminal ileum (13). Thus the bile acid pool shrinks progressively and bile flow is decreased, subsequently enhancing the cholestasis and liver damage.

Rintala et al. (15) showed that the intractable cholestasis associated with TPN may be treated by irrigation of the biliary tree. In experimental and clinical studies, it has been shown that TPNAC may be reversed by daily cholecystokinin injections (16-18). Both biliary tree irrigation and cholecystokinin injection stimulate the enterohepatic circulation. The presence of normal bile acids in portal triad from enterohepatic circulation may suppress the lipocytes either directly or via cytokines such as transforming growth factor beta. Evidence suggests that lipocytes are the primary mesanchymal cells responsible for pathogenic fibrosis (19). The cholestasis usually resolves when the infant resumes enteral nutrition (2). In some patients, as in our patients with jejunostomy, the institution of enteral feeding does not restore normal bile flow. In these cases, progressive liver damage, liver failure and death may be inevitable.

The fact that the development of TPNAC in all neonates who had jejunostomy suggests that one of the most important factors in the development of TPNAC is the interruption of enterohepatic circulation. In addition to the prevention of sepsis, avoidance of jejunal stoma, institution of enteral feeding as early as possible and restoration of enterohepatic circulation by various methods (e.g. irrigation of the biliary tree, cholecystokinin and ursodeoxycholic acid administration) may be useful for the prevention of cholestasis in neonates receiving long term TPN. Furthermore, the presence of jejunostomy may be a good model for studies to determine the correlation between TPNAC and enterohepatic circulation.

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