Parenteral Nutrition Induced Cholestasis in Neonate

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Abstract
Objectives: Parenteral nutrition (PN) is an important therapeutic modality for neonates with specialised situation. But PN induced cholestasis is a serious problem. To find out incidence, clinical and investigational profile and therapeutic modality in neonates the following study was done.

Method: Fifty neonates who were admitted in pediatric gastroenterology ward of PGIMER Chandigarh from July 1993 to June 2003 and developed PN induced cholestasis were enrolled for the study. Detailed clinical history, incidence of PN induced cholestasis, age, sex, gender of babies, IUGR status, duration of PN, types of PN fluid, LFT, biochemical profile like glucose, electrolyte, urea, creatinine, PTI etc. have been noted. Amino acid/dextrose/lipid emulsion solution/trace element etc. were given. Analysis of ABG/Hb%/glucose electrolytes/platelet/LFT/RFT/USG whole abdomen etc. were routinely done and correction was given accordingly. Enteral feeding with expressed breast milk was started on all cases.

Results: Out of 50 infants who received PN 30(60%) developed cholestasis. Male was 20 and female was 10. Premature babies (less than 37 weeks) was 35(70%), SGA was 20(40%), duration of PN was more than 2 weeks in 45(90%) cases. Surgical neonates (short gut syndrome following NEC, intestinal atresia, Hirschprung, gastroschisis etc.) were 5(10%). Out of 30 neonates- all developed rise of SGOT/SGPT, bilirubin. USG of 30 cholestatic babies shows hepatomegaly. Features of portal hypertension (e.g ascites, splenomegaly, GI bleed etc. were not seen in any case). PN was stopped temporarily when cholestasis developed. Enteral feeding with expressed breast milk was gradually increased. UDCA was given at a dose of 15mg/kg/day in two divided doses and antibiotics were given when indicated. Metabolic complication (e.g hypoglycemia, hyperglycemia, hypertriglyceridemia/sepsis etc. were taken care of.

Conclusion: PN induced cholestasis is a serious problem in neonate. Prematurity/SGA baby/male baby/high carbohydrate/lack of eternal feeding is risk factors. Maximally tolerated enteral nutrition/cyclic parenteral nutrition/omegaven/avoiding high carbohydrate solution are protective against PN induced cholestasis.

Keyword: Neonatal Parenteral nutrition, cholestasis.
of amino acid are various factors of PN induced cholestasis.\(^4\)(\(^5\) ) PN induced cholestasis is more common in male.\(^6\) Toxicity of phytosterols, trace mineral toxicity are important factors for PN induced cholestasis in neonate.\(^7\) In some cases progressive liver damage, liver failure and death can occur.\(^8\) Cholestasis is a very common complication of PN but its cause is not fully understood. It is multi factorial.\(^9\) Aggravating factor for PN induced cholestasis is sepsis\(^{10}\) and duration of bowel rest.\(^{11}\) Prematurity, low birth weight and duration of PN are often seen as risk factor for developing PN induced cholestasis.\(^{12}\)(\(^13\) ) The risk factors like duration of PN, prematurity, low birth weight are overlapping and inseparable from each other because premature and low birth weight babies often require prolonged parenteral nutrition.\(^{14}\) PN induced cholestasis is common in low birth weight infant who are either extremely premature or IUGR.\(^{15}\) In IUGR babies PN induced cholestasis is more common because of metabolic and physiological changes to hepatocytes secondary to utero placental insufficiency.\(^{16}\) IUGR babies have altered expression of glucose transporters leading to triglyceride deposition in liver.\(^{17}\) IUGR babies are more susceptible to infection. Sepsis facilitates PN induced cholestasis.\(^{18}\) Duration of PN is a risk factor for PN induced cholestasis in neonate.\(^{19}\)

**Method**

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**Results**

Out of 50 infants who received PN 30(60%) developed cholestasis. Male was 20 and female was 10. Premature babies (less than 37 weeks) was 35(70%), SGA was 20(40%), duration of PN was more than 2 weeks in 45(90%) cases. Surgical neonates (short gut syndrome following NEC, intestinal atresia, Hirschprung, gastroschisis etc). were 5(10%). Out of 30 neonates- all developed rise of SGOT/SGPT, bilirubin. USG of 30 cholestatic babies showed hepatomegaly. Features of portal hypertension (e.g ascites, splenomegaly, GI bleed etc. were not seen in any case). PN was stopped temporary when choestasis developed. Enteral feeding with expressed breast milk was gradually increased. UDCA was given at a dose of 15mg/kg/day in two divided doses and antibiotics were given when indicated. Metabolic complication (e.g hypoglycemia, hyperglycemia, hypertriglyceridemia/ sepsis etc.were taken care of.

**Discussion**

Lack of enteral stimulation is an important risk factor for PN induced cholestasis in neonate.\(^{20}\) It is thought to be due to reduction of growth factors secretion that promote enterocyte maturation.\(^{21}\) Intestinal stasis leads to intestinal bacterial overgrowth. Endotoxin of gram negative bacteria can inhibit bile secretion and lead to choestasis.\(^{22}\) Premature infants are more susceptible to endotoxemia.\(^{23}\) High content of carbohydrate in PN solution can lead to high incidence of PN induced choestasis. High carbohydrate leads to high triglyceride content in liver.\(^{24}\) High dextrose level in PN solution is correlated to alter level of insulin and glucagon in plasma. It leads to altered hepatocyte morphology and increased periportal fatty infiltration.\(^{25}\) It is recommended that dextrose in PN should not be more than 7gm/kg/day.\(^{18}\) Lipid is not recommended more than 2.5gm/kg/day in
parenteral nutrition. Lipid doses higher than 1gm/kg/day can lead to liver damage. Excess lipid is deposited in kupfer cells. The babies who receive omegaven (fish oil emulsion) after developing PN induced choestasis have higher rate of reversibility compared to those who receive soya based emulsion. Various animal study have shown that fish oil emulsion never impair bile secretion and always prevent steatosis. Soya based fat emulsion contains phyposterol that have been recently identified as primary offending agents in PN related cholestasis. Fish oil does not contain phyposterol but omega 3 polyunsaturated fatty acid which have known anti-inflammatory properties. We did not use fish oil lipid emulsion in any case. Cycling total parenteral nutrition (TPN) has been implemented as a method to minimize liver damage in neonates. We did not initiate cyclic PN in our 50 cases. The temporary cessation of amino acids and dextrose inflixion has been theorised to improve substrate utilisation and decrease lipogenesis within liver. The incidence of PN associated liver disease is directly related to duration of PN therapy. Cholestasis is reported as high as 85% in neonates requiring prolonged PN. Morbidity and mortality increase and directly correlate to degree of liver dysfunction. Cyclic or non continuous PN is strategy used to treat or prevent PN associated liver disease. The intermittent rather than continuous supply of amino acid/glucose will allow more efficient substrate utilisation resulting in metabolic normalcy. Cyclic PN is associated with improved liver transaminase, hepatic function and resolution of hepatomegaly. Cyclic PN seem to be most efficient in controlling mild to moderate liver disease. In infants cyclic PN lowers or stabilises serum bilirubin level. If used prophylactically, cyclic PN can lower incidence of hyper bilirubinemia. In surgical neonate, PN associated liver disease is related to prematurity, low birth weight, male gender, excess energy intake, absence of enteral feeding, sepsis, bowel surgery, length of resected bowel.

Hyperglycemia, hypoglycemia and hypertriglyceridemia are associated with increased mortality and morbidity in PN associated liver disease neonates. Potential benefit of early initiation of cyclic PN prior to development of liver disease in surgical neonate is noted. However overall moderately high incidence of hypoglycemia with cyclic PN warrants careful monitoring and consideration should be given for continuous PN. During parenteral nutrition it is not advisable to go above 18gm/kg/day of carbohydrate because this will lead to lipogenesis, increase co2 production, increased radical mediated lipid peroxide formation. Glutamine is good for TPN. Parenteral nutrition is indicated in birth weight babies <1kg/ birth weight between 1 to 1.5 kg babies if anticipated to be of insufficient feeding for 3 or more days/ more than 1.5 kg babies if anticipated to be insufficient feeding for 5 or more days/ surgical conditions like NEC/ gastrochisis/ omphalocele/ tracheoesophageal fistula, intestinal atresia, malrotation, shortgut syndrome, meconuem ileus etc. Home parenteral nutrition is initiated in infants having short bowel syndrome (SBS), (loss of anatomy or functional loss of more than 50% of small intestine length) following NEC/ mid gut volvulus / small intestinal atresia/ Hirsprung/ pseudo obstruction/microvillus atrophy. After adaptation, infant can tolerate more enteral feeding and PN is gradually weaned from 16 - 18 hours a night to 8 - 12 hours a night. We did not initiate home parenteral nutrition in any case. The most serious complication of home parenteral nutrition is choestatic liver disease. It is caused by small amount of enteral nutrition, repeated infection, receiving more calories through PN. Addition of taurine in TPN significantly reduces hepatic problem in neonates.

Conclusion
PN induced cholestasis is a serious problem in neonate. Prematurity/SGA baby/male baby/high carbohydrate/lack of eternal feeding are risk factors. Maximally tolerated enteral
nutrition/cyclic parenteral nutrition/ omevaven/ avoiding high carbohydrate solution are protective against PN induced cholestasis.

Conflict of interest – Nil

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