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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, Hirsprung, 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 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.*

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.*

Introduction

Parenteral nutrition (PN) induced cholestasis is a serious problem in neonate.[1] Exact cause of PN induced cholestatis is not known but it has multiple factors.[2] Low birth weight is an important cause of PN related cholestasis.[3] Prematurity, sepsis, long duration of PN (>2 weeks), lack of enteral feeding, quantity or quality

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 triglycerive 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

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, Hirsprung, 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 triglycerive 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.[26] Lipid doses higher than 1gm/kg/day can lead to liver damage.[27][28]
Excess lipid is deposited in kupfer cells.[29][30] 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.[31] Various animal study have shown that fish oil emulsion never impair bile secretion and always prevent steatosis.[32][33] Soya based fat emulsion contains phyposterol that have been recently identified as primary offending agents in PN related cholestasis.[14][26][34] 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.[36] We did not initiate cyclic PN in our 50 cases. The temporary cessation of amino acids and dextrose influsion has been theorised to improve substrate utilisation and decrease lipogenesis within liver.[37] The incidence of PN associated liver disease is directly related to duration of PN therapy.[38] Cholestasis is reported as high as 85% in neonates requiring prolonged PN.[39] Morbidity and mortality increase and directly correlate to degree of liver dysfunction.[40] 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.[41] Cyclic PN is associated with improved liver transaminase, hepatic function and resolution of hepatomegaly.[42] Cyclic PN seem to be most efficient in controlling mild to moderate liver disease.[43] In infants cyclic PN lowers or stabilises serum bilirubin level.[41]
If used prophylactically, cyclic PN can lower incidence of hyper bilirubinemia.[44] 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 ressected bowel.[45]
Hyperglycemia, hypoglycemia and hypertriglyceridemia are associated with increased mortality and morbidity in PN associated liver disease neonates.[46] 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.[47] 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.[48] 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/ gastroschisis/ omphalocele/ tracheo esophageal fistula, intestinal atresia, malrotation, shortgut syndrome, meconeum ileus etc.[49]
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.[50]
Addition of taurine in TPN significantly reduces hepatic problem in neonates.[51]

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/ omegaven/ avoiding high carbohydrate solution are protective against PN induced cholestasis.

Conflict of interest – Nil

Reference

1. Gastroenterology research and practice, Volume 2013 Article Id 163632 http://dx.doi.org/10.1155/2013/163632, Khein Joli- Dahel et al, Ottawa, Canada-KIH8L1
2. F.J Suchy, "Neonatal cholestasis" Pediatrics in review, Volume 25, no. 11, PP-388-396, 2004
3. TPN cholestasis in premature infants: The role of parenteral nutrition solution, Nancy F Sheard et al Pediatric annals. 1987:16(3):243-252, http://doi.org/10.3928/0090-4481-19870301-09
4. M. Steinbach et al Demographic and nutrition factors associated with prolonged cholestatic jaundice in premature infants. J. perinatology Volume28(2):129-135 2008
5. K. Wright et al, Increased incidence of parenteral nutrition associated cholestasis with aminosyn PF compare to trophamine, J. perinatology, Volume23(6):444-450, 2003
6. MJ. Albers et al, Male sex predisposes the new born surgical patients to parenteral nutrition associated cholestasis and to sepsis. Archieves of surgery, Volume 137(7), 789-793, 2002
7. PT Clayton et al, The role of phytosterol in pathogenesis of liver complication of pediatric parenteral nutrition, Vol.14(1), 158-164, 1998
8. A L Buchman et al, Parenteral nutrition associated liver disease and role for isolated intestinal and intestine/liver transplantation, Hepatology, Vol.47(1) 19, 2006
9. D R Duerksen, The parenteral nutrition impairs bile flow and alters bile composition in new born piglet, Digestive disease and science, Vol.41(9), 1864-1870, 1996
10. R H Moseley, Sepsis associated cholestasis, Gastroenterology, Vol.112(1), 302-306, 1997
11. J C Alverdy, Total parenteral nutrition promotes bacterial translocation from the gut, Surgery Vol.104(2), 185-190, 1998
12. E F Beale, Intrahepatic cholestasis associated with parenteral nutrition in premature infants. Pediatrics, Vol.64(3) 342-347, 1979
13. R J Merritt, Cholestasis associate total parenteral nutrition, J pediatric gastroenterology and nutrition Vol.05(1) 9-22, 1986
14. D A Kelly, Liver complication of pediatric parenteral nutrition, Epidemiology, Nutrition, Vol.14(1) 153-157, 1998
15. G Boehm et al, Influence of intra uterine growth retardation on parameter of liver function in low birth rate infants. European journal of pediatrics, Vol.149(6) 396-398 1990
16. G Boehm et al Metabolic difference between AGA and SGA infants of very low birth weight- relationship to intrauterine growth retardation Acta pediatr scand Vol.77(1) 19-23 1998
17. R H Laue et al Localization and quantification of glucose transporters in liver of growth retarded fetus and neonatal rat. Am. J physiology, endocrinology and metabolism, Vol.276(1) E 135-E142, 1999
18. F W Guglielmi et al, Cholestasis induced by total parenteral nutrition, Clinics in liver disease, Vol.12(1) 97-110 2008
19. S Suita et al, Follow up studies of children treated with long term intravenous nutrition (IVN) during neonatal period, J pediatric surgery, Vol.17(1), 37-42, 1982

20. J Alverdy et al, The effect of parenteral nutrition on gastrointestinal immunity. The importance of enteral stimulation, Annals of surgery, Vol.202(6), 681-684, 1985
21. A F Hofmann, Defective biliary secretion during total parenteral nutrition- probable mechanism and probable solution, J pediatric gastroenterology and nutrition, Vol.20(4) 376-390, 1995
22. R Utilu, Endotoxin effect on liver, Life science, Vol.20(4), 553-568, 1977
23. J C Reeney, Jaundice associated with bacterial infection in new born, Am.J of disease of children Vol.122(1),39-41, 1971
24. R Rager et al Cholestasis in immature new born infants. Is parenteral alimentation responsible? J pediatrics, Vol.86(2), 264-269, 1975
25. S Li et al Increasing dextrose concentration in total parenteral nutrition (TPN) causes ulternation on hepatic morphology and plasma level of insulin and glucagon in rats. J surgical research Vol.44(6) 639-648, 1988
26. V Colom, Role of lipid emulsion in cholestasis associated with long term parenteral nutrition in children, J parenteral and enteral nutrition, Vol.24(6), 345-350, 2000
27. M Cavicchi et al, Prevalance of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Annals. Internal med.2000, 132(7) april 4, 525-532
28. D B Alerdyce, Cholestasis caused by lipid emulsion, Surgery, gynaecol and obstetrics, Vol.154(5) 641-647, 1982
29. Y Koga, Hepatic intravenous fat pigments in infants and children receiving lipid emulsion, J pediatric surgery, Vol.10(5), 641-648, 1975
30. J H Parswell, Pigment deposition in retriculo endothelil system after fat emulsion infants. Archieves of disease of childhood, Vol.51(2), 135-139, 1992
31. K M Gina, Safety and efficacy of fish oil based fat emulsion in treatment of parenteral nutrition associated liver disease, Pediatrics, Vol.121(3), E678-E686 2008
32. I P J Alwyn et al, Omega 3 fatty acid improve hepatic steatosis in a murine model- potential implication for marginal steatotic liver donor, Transplatation, Vol.79(5), 606-608, 2005
33. J E Van Acrde, Intravenous fish oil emulsion attenuate parenteral nutrition induced cholestasis in new born piglets, Pediatric research, Vol.45(9), 202-208, 1999
34. P J Javid, The root of lipid administration effects parenteral nutrition induced hepatic steatosis in a murine model, J ped surgery Vol.40(9) 1446-1453, 2005
35. B Edgren, Theoretical background of intravenous nutrition with fat emulsion, Nutritio et dieta, Vol.5 364-386, 1963
36. J Slicker et al, Pediatric parenteral nutrition- putting the microscope on macro nutrients and micro nutrients, Nutr clin pract, 24(4), 2009, 481-486
37. T H Nehiem Rao et al, Rights and benefits of prophy lactic cyclic parenteral nutrition in surgical neonates. Nutri clin pract, Vol.28(6) 2013, 745-752
38. Wright K et al, Increased incidence of parenteral nutrition associated cholestasis with aminosyn PF compare to trophamine, J Perinatal 2003, 23(6) 444-450
39. Christensen R D et al, Identifying patients on the first day of life at high risk of developing parenteral nutrition associated liver disease, J perinatol 2007 (pubmed)
40. Hillis T C, High rate of mortality and morbidity occurring in infants with parenteral nutrition associated cholestasis, J Parenteral and enteral nutrition, 2010, Vol.34(1) 32-37 (pubmed)
41. Collier S et al, Use of cyclic parenteral nutrition in infants less than 6 months of

age, Nutrition in clinical practice, 1994, 9(2):65 (pubmed)

42. Effects of cyclic parenteral nutrition on parenteral associated liver dysfunction parameters Jose J. Arenas Villafranca et al, Nutrition journal 2017 16:66
43. Hawang T L et al, Early use of cyclic TPN prevents for the deterioration of liver function for TPN patients with impaired liver function, 47(35):1347-1350(pubmed) 2000
44. Jensen AR, The association of cyclic parenteral nutrition and decreased incidence of cholestatic liver disease in patient with gastroschisis, J pediatric surgery, 2009, 44(1), 183-189(pubmed)
45. Beath SVS, Parenteral nutrition related cholestasis in post surgical neonates-multicentric analysis of liver function, J pediatric surgery 1996, 31(4):604-606
46. Vannucci R, Hypoglycemic brain injury, Seminar in neonatology, 2001, 6(2) 147-155(pubmed)
47. Neutric clin prac 2013, Dec 28(6), 747-752, Risk and benefits of cyclic parenteral nutrition in surgical units.
48. Metabolism and nutrition in surgical neonate, Seminar pediatric surgery, 2008 (nov) 17(4), 276-284
49. AIIMS- nicu Protocol 2008
50. A home parenteral nutrition program for infants, Julia A Bilodeau et al Jognn Jan 1995, Vol.24(1)72-76
51. Cholestasis induced by total parenteral nutrition- effect of addition of taurine on hepatic failure parameters- possible synergistic action of structure lipids (SMO F lipid), J Gonzalez- Contreras et al, Nutrition hosp. 2012 Nov- Dec ;27(6):1900-7.