Original Articles

PARENTERAL NUTRITION (PN) IN THE MANAGEMENT OF VERY LOW BIRTHWEIGHT (VLBW) BABIES-A RANDOMIZED CONTROLLED TRIAL

Umesh V. Vaidya
Sheila A. Bhave
Anand N. Pandit

ABSTRACT

Eighty five very low birth weight (VLBW) babies with birthweight less than 1250g were randomly assigned such that 43 *received parenteral nutrition (PN) with aminoacid based glucose electrolyte solution (Vamin) and lipid emulsion (Intralipid) in the first 16 days of life. The other 42 (control group) received conventional intravenous dextrose with or without electrolytes plus enteral milk regimen. Baseline clinical parameters and neonatal problems encountered in the two groups were similar. There was no significant difference in the mortality rate in the two groups (48.9% in PN group and 42.9% in control group:* $X^2 = 0.3$, $p > 0.05$*). The commonest cause of mortality in both the groups was septicemia (163% and 26.1% in PN and control groups, respectively). Local complications, sepsis and fluid electrolyte disturbances were similar in the two groups. Azotemia (25.6%), hyperlipidemia (9.3%), metabolic acidosis (9.3%) and prolonged cholestasis (14%) were commoner in the PN group but were reversible with early recognition. Time taken to regain birthweight was also similar in the two groups (*$X^2 = 14.2$ *and 15.2 days for PN and control groups, respectively). Thus, PN failed to improve the survival or early weight gain in the routine management of the VLBW babies in our unit.*

Keywords: *Parenteral nutrition, Very low birthweight babies, Management.*

From the Department of Pediatrics, K.E.M. Hospital, Pune 411 011.

Reprint requests: Dr. Sheila Bhave, Department of Pediatrics, K.E.M. Hospital, Pune 411011.

Received for publication: December 21,1993; Accepted: November 7,1994

Wilmore and Dudrick in 1968 demonstrated a dramatic improvement in the outcome of severe short gut syndrome in children with long term PN(1). Since then, the technique has been enthusiastically tried in a number of surgical and medical conditions assocaited with feeding difficulties, small inten-stinal failure and/or severe malnutrition(2-4). Unfortunately, very few if any, controlled clinical trials have validated this enthusiasm. One such situation is the routine supplementation of parenteral nutrition (PN) in very low birth weight (VLBW) babies-in the United States, currently, most babies with birthweight <1500g receive PN as their sole or major source of nutrition for the first several days or even weeks of life(5).

With rapid advances in tertiary care neonatal medicine, PN is being set up at many centres in our country. However,

in view of the expense and expertise involved, it is necessary for us to have a clear idea of the value and indications of PN in neonates.

Over the past 6 years, PN has been used in over 100 children and neonates at our centre in KEM Hospital, Pune(6). Cost and complications have reduced significantly with continuous experience and indigenisation(7). The specific aim of this study was to evaluate the role of PN (if any) in the reduction of mortality and morbidity in the routine management of VLBW babies in our setting.

Subjects and Methods

Eighty five VLBW babies with birthweight <1250 g who survived the first 48 hours were randomly assigned to parenteral nutrition group (PN) or conventional intravenous fluid therapy (control group) in the first 15 days of life. Aminoacid solution (Vamin) was initiated on the 3rd day of life in a dose of 0.5 g/kg/day and increased daily upto a maximum of 3 g/kg/day. Lipid emulsion (Intralipid) was started on the 5th day of life in a dose of 0.5 g/kg/day and increased to a maximum of 3 g/kg/day. Lipid administration was deferred in babies with hyperbilirubinemia (serum bilirubin >10 mg/dl). Electrolytes, minerals and vitamins were added as per standard recommendations(8). Enteral feed in the form of expressed breast milk or formula (Dexolac, Wockhardt) was initiated and increased as per the tolerance with suitable fluid adjustments in parenteral feeds. Technique, protocol and monitoring of PN were as previously described(6,9).

Control group received intravenous 10% dextrose at 60 ml/kg on day 1, which was increased to 120-150 ml/kg by the end of the first week. Enteral feeds similar to PN group babies were started and advanced as per tolerance upto a maximum of 200 ml/kg/day with suitable reduction in intravenous fluids. Enteral feeds in both groups were by intermittent gavage feeding.

The outcome variables analysed in the two groups were mortality, morbidity and related complications. Sample size calculation was done using EPI INFO statistical software assuming an event rate (mortality) in the controls as 50% and expecting a 10% reduction in mortality in the PN group (one tailed test, 95% confidence limit). Chi square test and Fisher exact tests were used to test statistical significance in the two groups.

Results

Of the 85 VLBW babies (birthweight < 1250 g) enrolled for this study, 43 were included in the PN group and 42 in the control group, *i.e.,* conventional intravenous fluid plus enteral feeding group. There were no significant differences in the baseline variables (mean birthweight, gestational age and percent SGA) and in the neonatal problems encountered (respiratory distress syndrome apnea, hypoxic ischemic encephalapathy) in the two groups *(Table* I).

The mean duration of administration of PN was 8.7 ± 0.5 days (range 2-16 days). The mean maximal protein and lipid intakes in the PN group were 2.6 ± 1.2 and 3 ± 1.5 g/kg/day. All babies received PN by peripheral sites except for four, who required a central catheter (umbilical) because of non-availability of peripheral sites.

TABLE I-*Clinical Profile and Mortality of Babies in the Parenteral Nutrition and Control Groups*

Parameter		PN group (n=43)	Control group (n=42)
Birthweight (g)	Mean	1116±101	1081 ± 123
	Range	(900-1245)	(800-1250)
Gestational age	Mean	31.5 ±2.8	31.5 ± 3.2
(weeks)	Range	(28-40)	(28-40)
SGA(%)		58.1	54.7
Days required to	Mean	14.2± 10.3	15.2 ± 8.6
regain birthweight	Range	(0-41)	(0-33)
Mortality n (%)		21 (48.9)	18 (42.9)*
Cause of Mortality			
Septicemia		7	11
Intracranial hemorrhage		4	2
Pulmonary hemorrhage		5	1
Necrotizing enterocolitis (NEC)		-	2
Apnea		3	1
Hyaline membrane disease		2	1

* Chi square 0.3, p >0.05.

In the control group, the mean duration of intravenous fluids (10% dextrose) was 8.4 ± 6.7 days. The mean age at initiation and type of enteral feeding (expressed breast milk/formula) did not differ in the 2 groups (3.6 ± 3.5 days in PN group and 2.6 ±1.7 days in the control group).

There was no significant difference in the overall mortality rate in the 2 groups *(Table I).* Septicemia was the commonest cause of mortality in both the groups. The incidence of fatal intracranial and pulmonary hemorrhage was higher in the PN group, whereas NEC was responsible for death in two control babies as against none in the PN group. The mean duration of time to regain birthweight (after the initial postnatal weight loss) in the survivors was 15.2 ± 8.6 days (range 0-33 days) and 14.2 ± 10.3 days (range 0-41 days) for the control and the PN group, respectively (p >0.05).

The local and systemic complications encountered in the two groups are seen in *Table II.* There were no significant differences in the number of babies with complications due to infection and fluid imbalance. However, local and metabolic complications, particularly azotemia and hyperbilirubinemia were commoner in the babies receiving PN as compared to controls. All were

TABLE II–*Complications During the Study.*

Complications (n)	PN Group (n=43)	Control Group (n=42)
Local	12	7
Thrombophlebitis	7	5
Cutaneous gangrene	3	2
Abscess	2	-
Infective	5	7
Fluid Imbalance	2	3
Metabolic Abnormalities		
Electrolyte imbalance	2	4
Hypoglycemia	5	4
Hyperglycemia	2	1
Hyperbilirubinemia	11	7
Ca & PO_4 abnormalities	3	2
Azotemia	11	1
Hypertriglyceridemia* (>200 mg/dl)	4	-
Elevated transaminases*	2	-
Cholestasis*	6	-
Metabolic acidosis*	4	-
Others		
Thrombocytopenia	2	-
Bleeding diathesis	1	-

* Parameters monitored only in the PN group.

reversible with early recognition. Hyperlipidemia, seen in 4 VLBWs (9.3%) during fat administration, reduced rapidly by controlling the lipid intake. Cholestasis which occurred in 6 (14%) babies receiving PN continued for prolonged periods lasting for 13-286 days. This cholestasis (though prolonged), resolved spontaneously in all but one baby, who died of hepatic dysfunction at the age of 27 days with postmortem liver biopsy findings of giant cell transformation, hepatic necrosis and proliferation of bile ducts.

Discussion

A number of theoretical advantages suggest the indication of parenteral nutrition in VLBW babies. The various feeding difficulties, gastrointestinal immaturity and frequent occurrence of illnesses such as apnea and respiratory distress, hamper the initiation and establishment of adequate enteral feeding(3,10). At the same time the greatly increased demands and poor stores(11) are such that a 1000 g baby is not expected to survive beyond 7 days on intravenous fluids alone(12). It is, therefore, surprising that well designed clinical trials have failed to show convincing survival advantages of routine PN policy over conventional enteral feeding with or without intravenous fluids(5,13,14). In the present study too, there was no significant difference in the mortality in the two study groups, being over 40% in both *(Table I)*. The chief causes of death in both groups were also similar, *viz.,* septicemia, intracranial and pulmonary hemorrhage and respiratory distress with or without apnea. In the absence of other supportive measures such as ventilation, these conditions are known to have a poor outcome in VLBW babies with birthweight <1250 g(15,16). It is, therefore, perhaps, not fair to evaluate PN in VLBWs by mortality figures alone.

On the positive side, this study also demonstrates that the technique of PN, by itself did not confer a greater risk of mortality in this high risk group in our unit. Complication rates in the PN group too, were not significantly higher

than in control group. With stringent monitoring protocols and continuous training of staff, die PN related complications have reduced in our unit to rates comparable to western centres particularly, for sepsis(3,17), cholestasis(18) and metabolic disturbances(19,20). NEC did not develop in any of the PN group patients as against two in our control group and though the numbers are small, this observation has also been reported in the other similar controlled studies(13,14).

Though routine supplementation of PN in VLBW babies cannot be recommended on the basis of this study, it does not absolve NICUs from developing this important technique in their units. PN has already proven its critical life saving value in various neonatal conditions such as severe congenital anamolies of gut, NEC and intractable diarrheas(21,-23). In our unit too, the most gratifying results of PN were in surgical neonates with successful surgical corrections, *viz.,* tracheoesophageal fistula and duodenal atresia(6). Importantly, various studies have suggested atleast two compelling reasons for the use of PN in carefully selected situations: (i) PN is capable of supporting normal to supra normal rates of growth in LBW babies(24); and *(ii)* PN can be given for prolonged periods with only minimally added morbidity(25).

In conclusion, routine supplementation of PN in VLBW babies for the first week or two of life offers no survival advantage or disadvantage over a policy of enteral feeding plus intravenous fluids. Safe parenteral feeding back up services, however, must be available in situations were enteral feeding is precluded for prolonged periods.

Acknowledgements

Grateful acknowledgement is made to the Indian Council of Medical Research for funding this trial. Acknowledgement is also made to Miss Mrinal Dhekne (Biochemist) and the nursing staff of the neonatal unit for their assistance in biochemical monitoring and administration of parenteral nutrition fluids to the babies in the trial.

REFERENCES

1. Wilmore DW, Dudrick SJ, Growth and development of an infant receiving all nutrients exclusively by veins. JAMA 1968, 203: 860-864.
2. Scot KE, Duncan J, Belgaumkar TK. Role of intravenous nutrition in reduction of premature infant mortality. Clin Res 1970,18:741-746.
3. Shaw JCL. Parenteral nutrition in the management of the sick low birthweight infant. Pediatr Clin North Am 1973, 20: 333-339.
4. Lloyd-Still JD, Shwachmann H, Filler RM. Protracted diarrhea of infancy treated with intravenous alimentation: 1. Clinical study of 16 patients. Am J Dis Child 1973,125: 358-368.
5. Heird WC. Parenteral feeding. *In:* Effective Care of the Newborn, 1st edn. Eds Sinclair JC, Bracken MB. Oxford University Press, 1992, pp 141-160.
6. Bhave SA, Vaidya UV. Parenteral nutrition in developing countries: Problems and Perspectives. *In:* Recent Advances in Pediatrics, Vol 4. Ed. Gupte S. New Delhi, Jaypee Publish ers, 1993, pp 106-121.
7. Vaidya UV, Hedge VM, Bhave SA, Pandit AN. Reduction of parenteral nutrition—related complications in the newborn. Indian Pediatr 1991, 28: 477-484.

8. Simmons CF. Fluid and electrolyte management in the newborn. *In:* Manual of Neonatal Care, 3rd edn. Eds Cloherty JP, Stark AR. Boston, Little Brown and Co., 1993, pp 457-467.

9. Bhave SA, Vaidya UV. Parenteral nutrition in the newborn: Technique and protocol. Bull Nat Neonatology forum 1992, 6: 1-7.

10. Easton LB, Halata MS, Dweck, HS. Parenteral nutrition in the newborn: A practical guide. Pediatr Clin North Am 1982, 29:1171-1190.

11. Crouch JB, Rubin LP. Nutrition. *In:* Manual of Neonatal Care, 3rd edn. Eds. Cloherty LP, Stark AR. Boston, Little Brown and Co., 1993, pp 526-558.

12. Heird WC, Driscoll JM, Schullinger JN, Grebin B, Winters RW. Intravenous alimentation in pediatric patients. J Pediatr 1972, 80: 351-372.

13. Glass EJ, Hume R, Long MA, Forfar JO. Parenteral nutrition compared with transpyloric feeding. Arch Dis Child 1984, 59:131-135.

14. Yu VYH, James B, Hendry P, Macmohan RA. Total parenteral nutrition in very low birthweight infants: A randomized controlled trial. Arch Dis Child 1979, 54: 653-661.

15. Bhakoo ON, Khajuria R, Desai A, Narang A. Lessons from improved neonatal survival at Chandigarh. Indian Pediatr 1989, 26: 234-240.

16. Singh M, Deorari AK, Paul VK, Mittal M, Shankar S, Munshi U, Jain Y. Three year experience with neonatal ventilation from a tertiary care hospital in Delhi. Indian Pediatr 1993,30: 783-790.

17. Beganvoic N, Vanhorick SPV, Brand R, Ruys JH. Total parenteral nutrition and sepsis. Arch Dis Chid 1988, 63: 66-67.

18. Farell MK, Balistreri MD. Parenteral nutrition and hepatobiliary dysfunction. Clin Perinatol 1986,13:197-212.

19. Heird WC, Dell RB, Driscoll JH. Grebin B. Metabolic acidosis after intravenous alimentation in pediatric patients. Pediatrics 1972, 80: 351-353.

20. Pildes RS, Ramamurthy RS, Cordero GV. Wong PWK. Intravenous supplementation of L-aminoacids and dextrose in low birthweight infants. J Pediatr 1973, 82: 945-950.

21. Gunn T, Bram RS, Pencharz PB, *et al.* Total parenteral nutrition in malnourished infants with intractable diarrhea. AMAJ 1977,117: 357-360.

22. Hyman CJ, Reiter J, Rodman J, *et al.* Parenteral and oral alimentation in the treatment of nonspecific protracted syndrome of infancy. J Pediatr 1971, 28:17-20.

23. Klish WJ, Putnam TC. The short gut. Am J Dis Child 1981,135:1056.

24. Zletkin HS, Bryan MH, Anderson GH. Intravenous nitrogen and energy in takes required to duplicate nitrogen accretion in prematurly born human infants. J Pediatr 1981, 99:115-120.

25. Candy DCA. Parenteral nutrition in pediatric practice. J Human Nutr 1980, 34: 287-296.