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Early versus Late Parenteral Nutrition in Very Low Birthweight Neonates

A retrospective study from Oman

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التغذية الوريدية المبكرة مقابل المتأخرة في حديثي الولادة ناقصي الوزن جدا

دراسة استعادية من عُمان

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الملخص: **الهدف**: مقارنة معالم الكيمياء الحيوية وزيادة الوزن وقلّة العظم ومكمّلات الفوسفات عند حديثي الولادة ناقصي الوزن جدا الذين يتلقون التغذية الوريدية المبكرة مقابل تلك التي تُعطى في وقت متأخر. **الطريقة**: أجريت دراسة استعادية في المستوى الثالث لوحدة العناية المركزة لحديثي الولادة في مستشفى جامعة السلطان قابوس، عُمان، للفترة من يناير 2007 إلى أكتوبر 2008 حيث أعطيت التغذية الوريدية المتأخرة ل 47 طفلا، بينما كان عدد الأطفال الذين أعطوا تلك التغذية بوقت مبكر 44 خلال الفترة من يناير 2009 إلى يونيو 2010. تم استخراج البيانات الديموغرافية والقياسات البشرية والمعالم المختبرية من نظام السجل الإلكتروني. **النتائج**: كان متوسط عمر البدء بالتغذية الوريدية في وقت مُتأخر 47.3 ساعة مقابل 14.3 ساعة.وكشف تحليل المعالم الكيميائية الحيوية خلال الأسبوع الأول من الحياة انخفاضا في فَرْط صوْديُوم الدَّم (12.7% مقابل 6.8%) وفرط بوتاسيوم الدم ليس بسبب قلة التبول (12.7 مقابل 6.8%) عند الأطفال ذوي التغذية الوريدية المبَكرة، مع عدم وجود اختلافات مُعتدّة في مستويات اليوريا والحماض بين المجموعتين. كان ارتفاع السكر في الدم> 12 ملمول/لتر في >1000غرام أعلى في التغذية الوريدية المبكرة. وكشفت المعالم الغذائية في 81 طفلا من الذين استطاعوا العيش/بقوا في وحدة الإنعاش حتى سن الحمل المصحّح وهو 34أسبوعا (40 في التغذية الوريدية المتأخرة و 41 في التغذية الوريدية المبكرة) انخفاضا في أمراض العظام الأيضية (قلة العظم عند الخُدّج، 17.5% مقابل7.3%)، والحاجة إلى مكملات الفوسفات (22.5% مقابل 7.3%) عند الأطفال ذوي التغذية الوريدية المبكرة. لم يكن هناك زيادة في الحماض أو ركود صفراوي. لم يلاحظ أي اختلاف في مستويات الزلال (الألبومين)، ووقت التغذية الكاملة ووقت استعادة الوزن عند الولادة ومتوسط زيادة الوزن لكل يوم حتى 34 أسبوعا من سن الحمل المصحّح. **الخلاصة**: يستطيع حديثي الولادة ناقصي الوزن جدا تَحمّل التغذية الوريدية المبكرة، التي تعمل على تقليل فرط الصوديوم في الدم، وتقليل فرط بوتاسيوم الدم غير الناتج عن قلة التبول، وأخيرا تقليل الحاجة إلى مكملات الفوسفات.

مفتاح الكلمات: رُضّع، حديثي الولادة، تغذية وريدية، فرط صوديوم الدم، فرط بوتاسيوم الدم، أمراض العظام، الوزن المنخفض جدا عند الولادة، عُمان.

ABSTRACT: ***Objectives:*** The aim of this study was to compare the biochemical parameters, weight gain, osteopenia and phosphate supplementation in very low birth weight (VLBW) neonates receiving early versus late parenteral nutrition (EPN versus LPN). ***Methods:*** A retrospective study was undertaken in the level III Neonatal Intensive Care Unit at Sultan Qaboos University Hospital, Oman: from January 2007 to October 2008 (LPN group, n = 47) and from January 2009 to June 2010 (EPN group, n = 44). Demographic data, anthropometric and laboratory parameters were extracted from the electronic record system. ***Results:*** The mean age of PN initiation was LPN = 47.3 hours versus EPN = 14.3 hours. Biochemical parameters analysed during the first week of life revealed a reduction in hypernatraemia (12.7% versus 6.8%) and non-oliguric hyperkalemia (12.7% versus 6.8%) in EPN, with no significant differences in acidosis and urea levels between the two groups. Hyperglycemia >12 mmol/L in <1000g was higher in EPN. Nutritional parameters in 81 babies who survived/stayed in the unit up to a corrected gestational age (CGA) of 34 weeks (40 in LPN and 41 in EPN), revealed a reduction in metabolic bone disease (osteopenia of prematurity [OOP], 17.5% versus 7.3%) and the need for phosphate supplementation (22.5% versus 7.3%) in the EPN group. There was no increase in acidosis or cholestasis. No difference was noted in albumin levels, time to full feeds, time to regain birthweight and mean weight gain per day till 34 weeks corrected CGA. ***Conclusion:*** EPN in VLBW newborns is well tolerated and reduces hypernatraemia, non-oliguric hyperkalemia, OOP and the need for phosphate supplementation.

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Keywords: Infants, newborn; Parenteral nutrition; Hypernatremia; Hyperkalemia; Bone disease; Very low birth weight; Oman.

Advances in knowledge

1. *Preterm birth results in sudden cessation of nutritional supply for which total parenteral nutrition (TPN) has been used in very low birth weight (VLBW) babies for years.*
2. *Currently, there is a move to introduce parenteral nutrition (PN) soon after birth to reduce the nutritional deficits occurring in the first days of life.*
3. *The time of commencement of PN in VLBW babies is still controversial and limited studies are available on the safety of early PN (EPN) in these babies.*
4. *Our study shows that EPN in VLBW is safe and does not cause metabolic derangement or increased incidence of acidosis.*
5. *In addition, we observed a reduced incidence of hypernatraemia, non-oliguric hyperkalemia and the need for phosphate supplementation in these babies.*

Application to patient care

1. *EPN for VLBW babies will provide better nutrition as compared to the conventional and current mode of initiating parenteral nutrition.*
2. *Our study shows EPN specifically reduces the incidence of metabolic derangements in the first week of life.*
3. *As parenteral nutrition is not available at weekends and holidays, we overcome this by having a starter TPN, which is stable when stored at 2–8°C for 30 days.*
4. *Approximately 3,000 VLBW are born in Oman each year and all these babies may benefit from EPN.*
5. *Provision for starter TPN should be made in all neonatal units.*

Premature very low birthweight (VLBW) infants miss out on fetal accretion of nutrients in the last trimester and have slow postnatal weight gain.[1] They are traditionally started on a dextrose infusion and graded to parenteral nutrition (PN) over several days. The goal of EPN is to provide an intravenous substrate that promotes protein deposition and increased lean body mass that approximates fetal growth rate and accretion. In recent years, early introduction and aggressive advancement of PN have been shown to be safe and effective.[2,3] Protein delivery of 3 gm/kg beginning on day one (D1) of life is safe and associated with plasma AA concentrations similar to those of second and third trimester fetuses.[4] In the absence of iatrogenic causes of electrolyte and acid base derangements, significant individual variations in nutritional requirements of preterm neonates from PN are rare.[5] Hypothesising that premature infants might benefit from the anabolic effects of EPN without metabolic derangement, we investigated the benefits of EPN in VLBW neonates. The objectives of our study were to compare the following between the EPN and LPN groups: 1) Biochemical disturbances in the first week of life; 2) Weight gain/day, mean weight at 34 weeks corrected gestational age (CGA), time to full feeds and time to regain birth weight, and 3) Incidence of osteopenia, the need for phosphate supplementation, cholestasis and albumin levels.

Methods

Inborn neonates, admitted to the neonatal intensive care unit (NICU) at Sultan Qaboos University Hospital (SQUH), Oman, were retrospectively studied over a period of 42 months from 1st January 2007 to 30th June 2010. The time periods were classified as epoch I, LPN (1st January 2007 to 31st October 2008) and epoch 2, EPN (1st January 2009 to 30th June 2010). The period from 1st November 2008 to 31st December 2008 was considered a transition period for unit policy change from LPN to EPN.

The study included all inborn VLBW babies between and including gestational age 25–32weeks and weighing ≤1500 g; those that survived >7days for assessing biochemical parameters; infants who survived/stayed in the NICU until corrected gestational age (CGA) of 34 weeks for assessing nutritional parameters, and who received PN for >5 days. Excluded from this study were infants with chromosomal and major congenital anomalies; those on PN for >4weeks; babies who died <7 days of age, and cases requiring surgery.

LPN group babies were started on intravenous dextrose soon after birth. Amino acid (AA),

Table 1: Composition of starter total parenteral nutrition

Contents	Quantity per 100 ml
Carbohydrates (g)	10
Amino acid (g)	2
Sodium (mmol)	1.55
Potassium (mmol)	0
Calcium (mmol)	1
Phosphate (mmol)	1.16
Acetate (mmol)	0
Magnesium (mmol)	0.25
Heparin (units)	100
Trace elements (ml)	0.66
Chloride (mmol)	1.14

(Primene 10%, Baxter, Newbury, UK) and intralipid (IL) emulsion 20% (Fresenius Kabi AB, Uppsala, Sweden) were started after day 2 of life, at the discretion of the neonatal team. The prescribing guideline for protein intake was a daily stepwise increment from 0.5 gm/kg/day up to a maximum of 3 gm/kg/day. The IL was commenced on day 2 at 1 gm/kg/day and increased by 1 gm/kg/day to a maximum of 3 gm/kg/day. Total fluid intake was 80 ml/kg/day on day 1 and increased by 20 ml/kg/day, up to a maximum of 150 ml/kg/day. EPN group babies were started on AA as soon as possible after birth. On day 1, the AA intake was 1.6 g/kg/day, day 2 was 2 g/kg/day and was increased to 2.5 g/kg/day on day 3 and on day four to 3 g/kg/day. The IL was started at 1 gm/kg on D1, increased to 2gm/kg on D2 and 3gm/kg on D3. Fluid intake was similar to the LPN group.

During the transition period, all clinical staff and faculty were instructed on the new standard of care and to commence starter TPN as the first fluid immediately after birth. The starter TPN formulation can be seen in Table 1. As the hospital pharmacy works five days a week, TPN was therefore unavailable for babies born after working hours, or during weekends and holidays. To overcome this problem a "starter" TPN was prepared. When kept at 2–8℃ this has a stability of 30 days. This was kept in the main pharmacy fridge for use as necessary by NICU staff at any time. The IL was preserved as 50 ml aliquots, which are stable for 1 week, for use as necessary.

Feeding of the infants was trophic, with expressed breast milk commenced on day 2 or 3 if the baby was stable. Increments of 2 ml were made every 24 hours after the first week. On the rare occasions when breast milk was unavailable, full term formula was used until full feeds were attained. Pooled breast milk is not an option in Oman. Most babies would reach full feeds by day 14. Direct breast feeding was attempted when babies reached 34 weeks CGA. In the case of hyperglycemia (>12 mmol/L), a continuous insulin infusion was started at 0.05 u/kg/hr and titrated to achieve normoglycemia.

In the study period, there were no major changes in antenatal care, NICU regimens or protocols that could influence the study outcome. The study was approved by the SQUH Ethics Committee. Individual consent was not considered necessary as it was a retrospective study on de-identified data.

Patients were identified from a computerised database. The standardised data extraction form included birth weight, gestational age, gender and Apgar score. Biochemical data were collected from birth through the first 7 days of life. These included mean urea, creatinine, bicarbonate and sodium. Biochemical parameters of interest were prevalence of hyperglycemia (blood glucose level >7 mmol/L and >12 mmol/L), non-oliguric hyperkalemia ([NOHK] serum K+ >6.5 mEq/L), hypernatraemia (Na+ >150 mmol/L). Nutritional data included age at start of PN, lowest mean phosphate and lowest mean albumin levels. Outcomes of interest included age in days at return to birth weight; weight gain per day; weight at 34 weeks; time to reach full feeds; osteopenia of prematurity (OOP) defined by ALP (alkaline phosphatase) >600 U/L; the need for phosphate supplementation (supplemented when phosphate values reached <1.8 mmol/L on oral feeds), and cholestasis (direct bilirubin >34 mmol/L or >15% of total bilirubin). Weight gain per day was computed as the difference in weight at 34 weeks and the birth weight divided by number of days.

The Statistical Package for Social Sciences (SPSS, Version 16, IBM, Chicago, Illinois, USA)) software was used to analyse the data. Statistical analysis was based on the conservative intention-to-treat approach. Differences in the proportions of categorical variables were assessed by chi-square analysis. Fisher's exact test was used in case of contingency tables with small counts. For the

Table 2: Demographic data of the subjects receiving late parenteral nutrition (LPN) or early parenteral nutrition (EPN)

Parameters	Epoch 1 (LPN) (n = 54)	Epoch 2 (EPN) (n = 49)	*P* value
Male, n	35	21	0.23
Female, n	19	28	0.19
BW <1000g	24	18	0.04
Mean BW (kg)	1.1	1.1	0.91
Median GA (weeks)	27	28	0.82
AGA, n	41	42	0.65
SGA, n	13	7	0.04
Mean 5 min Apgar	7.8	7.6	0.79
Mean TPN start (hrs)	47.3	14.3	0.05
TPN start ≤24 hrs, n	7	44	0.001
TPN start >24hrs, n	47	5	0.003

Legend: BW = birth weight; GA = gestational age; AGA = appropriate for gestational age; SGA = small for gestational age; TPN = total parenteral nutrition.

assessment of difference in means of continuous variables the Student t-test and Mann-Whitney test were performed as parametric and non-parametric tests, respectively. A *P* value of <0.05 was used as a cut-off for all tests of statistical significance.

Results

There were a total of 163 babies born at ≤32 weeks and ≤1500 g during the study period. Of these a total of 48 babies (29 in the LPN group, 19 in the EPN group) were excluded as they did not fit into the inclusion criteria: 15 babies were born at <25 weeks, 10 died at <7 days, 13 received PN for <5 days, 4 received PN for >28 days and 6 had major congenital anomalies. A total of 12 babies were excluded as they were born during the transition period; hence, a total of 103 neonates (54 in LPN and 49 in EPN) were enrolled in the study. Based on a national estimate of VLBW prevalence of 6.1 per 1,000 live births,[6] a sample size of 128 neonates was obtained in order to have 90% power of detecting a 20% difference in body weight between intervention and control groups at an alpha of 0.05. For the total enrollees in the study (103 neonates), the study maintained 84% power at alpha and beta levels of 0.05 and 0.2, respectively. The demographic data are shown in Table 2. There were no significant differences in the birth weight, gestational age, 5-minute Apgar scores, or male:female ratio in both groups. The majority of babies on LPN (87%) were started on TPN at >24 hours in comparison to EPN where TPN was started at <24hrs for the majority (89.8%). A total of 7 out of 54 babies in LPN and 5

Table 3: Day wise ideal protein, total caloric non-protein nitrogen (NPN) intake in early and late parenteral nutrition (EPN and LPN) groups per kg body weight

Day	Contents	EPN		LPN		*P* value
		g/kg	kCal/kg	g/kg	kCal/kg	
1	Glucose	8	27.2	8	27.2	
	Protein	1.6	6.4	-	0	1.0
	Lipids 20%	1	12	-	0	
	Total	-	45.6	-	27.2	0.04
	NPN	-	39.2		27.2	0.05
2	Glucose	10	34	10	34	
	Protein	2	8	0.5	2	0.001
	Lipids 20%	2	24	1	12	
	Total calories	-	66	-	48	0.17
	NPN	-	58	-	46	0.67
3	Glucose	12	40.8	12	40.8	
	Protein	2.5	10	1	4	0.05
	Lipids 20%	3	36	2	24	
	Total calories	-	86.8	-	68.8	0.06
	NPN	-	76.8	-	64.8	0.09
4	Glucose	14	47.6	14	47.6	
	Protein	3	12	1.5	6	0.04
	Lipids 20%	3	36	3	36	
	Total calories	-	95.6	-	89.6	0.71
	NPN	-	83.6	-	83.6	0.87
5	Glucose	15	51	15	51	
	Protein	3	12	2	8	0.19
	Lipids 20%	3	36	3	36	
	Total calories	-	99	-	95	0.92
	NPN	-	87	-	87	1.0

Day	Contents	EPN		LPN		*P* value
		g/kg	kCal/kg	g/kg	kCal/kg	
6	Glucose	15	51	15	51	
	Protein	3				
	12	2.5	10	0.88		
	Lipids 20%	3	36	3	36	
	Total calories	-	99		97	0.83
	NPN	-	87		87	1.0
7	Glucose	15	51	15	51	
	Protein	3				
	12	3	12	1.0		
	Lipids 20%	3	36	3	36	
	Total calories	-	99		99	1.0
	NPN	-	87		87	1.0

out of 49 babies in EPN were excluded as the time of commencement of TPN was not followed as per the objective of the study. Hence, 44 babies in the EPN group and 47 babies in the LPN group were considered for further analysis. The mean age at initiation of TPN was much earlier in EPN (14.3 hrs) compared to LPN (47.3 hrs) and this was statistically significant. Information on ideal total calorie intake per kg/day and non-protein nitrogen (NPN) intake in the EPN and LPN groups is given in Table 3. In each of the first 5 days of life, energy intake was greater in the EPN group. The AA supplementation was significantly higher in the EPN group on D2, 3 and 4 compared to the LPN group.

The biochemical parameters for the first 7 days are shown in Table 4. The incidence of hyperglycemia (>7 mmol/L) was similar in the two groups; however, a higher number of babies in EPN had hyperglycemia >12 mmol/L requiring insulin infusion. The mean urea, creatinine, sodium and bicarbonate levels were similar in the 2 groups. The incidence of hypernatraemia and NOHK was significantly higher in LPN group. The weight gain pattern, incidence of osteopenia, need for phosphorus supplementation, mean albumin level and incidence of cholestasis are shown in Table 5.

Seven babies in the LPN group and 3 babies in the EPN one were excluded for assessment of their nutritional parameters. In the LPN group, three of the excluded babies died in the late neonatal period and 4 babies were moved to other hospitals beyond the early neonatal period for various reasons. In the EPN group, 3 babies could not be included as they died in the late neonatal period.

The time to regain birth weight, the mean weight gain per day till 34 weeks, the mean weight at 34 weeks CGA were noted to be similar between the 2

Table 4: Biochemical parameters in early and late parenteral nutrition (EPN and LPN) in the first week of life

	LPN			EPN			*P* value
	<1000g	≥1000g	All	<1000 g	≥1000g	All	
	n = 14	n = 33	n = 47	n = 23	n = 21	n = 44	
Hyperglycaemia (>7mmol/L) n (%)	9 (64.2)	15 (45.4)	24 (51.0)	16 (69.5)	9 (42.8)	25 (56.8)	0.79
Hyperglycaemia (>12mmol/L) n (%)	1 (7.1)	1 (7.1)	2 (4.2)	6 (26)	1 (4.7)	7 (14.8)	0.03
Mean urea (mmol/L) mean (SD)	7 (3.1)	4.5 (2.5)	5 (3.0)	6.6 (2.4)	5 (2.0)	6 (2.3)	0.81
Mean creatinine (umol/L), mean (SD)	79 (18)	63 (13.8)	68 (16.6)	72 (14.0)	61 (13.2)	67 (14.5)	0.43
Mean sodium (mmol/L) mean (SD)	145 (4.9)	144 (4.2)	145 (4.2)	147 (3.8)	144 (2.5)	146 (3.5)	0.21
Hypernatraemia n (%) (>150 mmol/L)	2 (14.2)	4 (12.1)	6 (12.7)	3 (13)	0	3 (6.8)	0.04
NOHK, n (%) (.6.5 mEq/L)	2 (14.2)	4 (12.1)	6 (12.7)	3 (13)	0	3 (6.8)	0.02
HCO_3, (mmol/L) mean (SD)	19 (2.1)	17.8 (2.4)	18 (2.4)	16.4 (2.2)	18 (1.5)	17.3 (2.2)	0.54

Legend: SD = standard deviation; NOHK = non-oliguric hyperkalemia; HCO_3 = bicarbonate.

Table 5: Nutritional parameters in early versus late parenteral nutrition (EPN versus LPN)

	LPN			EPN			*P* value
	<1000g	≥1000g	All	<1000g	≥1000g	All	
	n = 11	n = 29	n = 40	n = 20	n = 21	n = 41	
Time to BW (days of life) mean (SD)	13.6 (4.3)	12.8 (4.8)	13 (5.1)	12 (5.7)	11 (3.3)	11.6 (4.6)	0.30
Time to full feeds (days of life) mean (SD)	22.5 (8.8)	11.8 (6.0)	14.7 (8.3)	21 (7.9)	12 (7.1)	16.3 (8.6)	0.89
MW gain/day till 34 weeks CGA (gms)	12.1 (4.9)	12.4 (3.8)	12.3 (4.1)	14 (3.8)	12.8 (5)	13.3 (4.5)	0.93
MW at CGA 34 (gms) mean (SD)	1479 (357)	1622 (163)	1583 (237)	1533 (310)	1720 (186)	1628 (268)	0.47
Lowest mean P(mmol/L) mean (SD)	0.92 (0.3)	1.2 (0.21)	1.1 (0.28)	1.4 (0.44)	1.9 (0.16)	1.6 (0.42)	0.14
OOP, n (%)	2 (18.1)	5 (17.2)	7 (17.5)	2 (10)	1 (5)	3 (7.3)	0.06
P supplements, (%)	4 (36.1)	5 (17.2)	9 (22.5)	2 (10)	1 (5)	3 (7.3)	0.04
Mean albumin (g/L) mean (SD)	24.5 (2.5)	28.3 (3.84)	27.3 (3.91)	24.5 (3.37)	29 (3.74)	27 (4.16)	0.75
Cholestasis, n (%)	2 (18.1)	3 (10.3)	5 (12.5)	3 (15.1)	2 (9.5)	5 (12.1)	0.96

Legend: BW = birth weight; SD = standard deviation; MW = mean weight; CGA = corrected gestational age; OOP = osteopenia of prematurity; P = phosphate.

groups. The phosphate level was better maintained in the EPN group compared to the LPN one, but this was not statistically significant. The incidence of OOP was higher in the LPN group especially in the subgroup 1–1.5 kg; however, the overall incidence was statistically insignificant.

The number of babies requiring phosphate supplementation was significantly higher in the LPN group (22.5%) compared to the EPN one (7.3%). The mean albumin levels and the incidence of cholestasis were similar in the 2 groups.

Discussion

TPN plays an important role in the nutritional support of preterm newborns while enteral feeds are gradually being increased. Data suggest that long term developmental outcomes in preterm babies may be correlated with early protein intake.[7] It has been shown that an aggressive intake of AA and IL can be tolerated immediately after birth.[8] Early administration of AA has been shown to be safe and promotes positive nitrogen balance in preterm infants.[2,9]

Some authors have studied the relationship of EPN with the weight gain in preterm infants. A prospective study by Valentine *et al.* compared 308 preterm VLBW infants who received EPN supplementation with 132 infants who did not receive EPN.[1] They observed improved weight gain in the EPN group, suggesting that nutrition that includes AAs may be critical during the first 24 hours of life. It was also observed that infants in the EPN groups had a shorter duration of TPN administration and achieved full enteral feeds earlier despite being smaller and younger. In another study, designed to evaluate preterm infant weight gains at 28 days after AA supplementation, infants were randomly assigned to receive 3.5 or 2.5 g/kg/day of AA. The higher intake of protein resulted in greater AA levels, but no difference was observed in weight gain at 28 days (12.9 g versus. 11.4 g respectively).[10] Ibrahim compared the nitrogen balance of EPN versus LPN in VLBW neonates. All infants in the LPN group had a negative nitrogen balance during the first 48 hours of life, while those in the EPN group had a positive balance throughout the seven-day study period.[8] In the present study, the use of starter TPN for administering EPN resulted in a significantly higher intake of AA in the first week of life [Table 3].

In our study, no significant differences were noted in the mean weight gain per day, mean weight at 34 weeks and time to reach full feeds. In both

groups, the weight gain and the weight at 34 weeks were less than if they had stayed in their intrauterine environment. This fall in growth despite EPN supplementation may mean that these babies were still protein limited. Although early administration of 1.5 g/kg of AAs can minimise or prevent the loss of protein stores, significantly higher intake is needed to promote growth[11] although Clarke showed no benefit of higher AA intakes.[10]

Hyperglycemia is frequent in VLBW infants. Murdock, *et al.* showed that early introduction of AA and lipids lowers serum blood glucose levels.[12] They suggested that decrease in blood glucose might be due to the stimulatory effect of AA on insulin secretion. Thureen demonstrated higher insulin concentrations in infants receiving AA at 3 gm/kg/day compared to those receiving 1 gm/kg/day.[4] Ibrahim showed statistically significant lower serum glucose levels in the EPN group compared to the LPN group, though both groups had serum glucose concentrations within normal ranges.[8] In our study, the incidence of hyperglycemia (>7 mmol/L) was similar in the 2 groups. This was consistent with the observation of Blanco;[13] however, in our case more babies in the EPN group had hyperglycemia (>12 mmol/L) and required insulin infusion.

Urea levels have been correlated with AA intakes in VLBW babies. Radmacher demonstrated a modest increase in urea as the AA dose was increased.[9] Blanco demonstrated higher urea levels in the early high amino acid (EHAA) group as compared with the standard amino acid (SAA) group during the first week of life.[13] Braake showed that in conjunction with the higher blood urea nitrogen (BUN) levels, the higher amounts of excreted nitrogen in the EHAA group indicated a higher oxidation rate.[2] Urea is a byproduct of AA oxidation and hence higher BUN levels in the absence of renal dysfunction should not be interpreted as a sign of intolerance, but as a reflection of AA utilisation. Our study showed no correlation between AA intake and the mean blood urea levels, which was consistent with the findings of Thureen.[4] It may be due to comparatively lower levels of AA supplementation.

Metabolic acidosis is common in the VLBW population in the first days of life and may be secondary to a variety of causes (usually between days 2—5) irrespective of dose and duration of AA administration.[14] Wargo concluded that a total chloride load in excess of 6 mEq/kg/day in LBW infants on TPN is associated with metabolic acidosis,[15] and improvement in the acid base status was demonstrated when the PN chloride had been replaced with acetate.[16] Our results did not reveal a higher incidence of acidosis in EPN. This may be explained by the low content of chloride in the starter TPN solution (1.14 mmol/100ml) and the fact that acetate was added as required in both epochs at the discretion of the attending neonatal team.

Disturbances in the fluid and electrolyte balance occur frequently in preterm infants as a result of high insensible water loss and renal immaturity, resulting in higher incidence of hypernatraemia and hyperkalemia.[17] Elstgeest compared serum sodium values in the first 3 days of life in two cohorts of infants (<28weeks gestation who received early and late TPN) and found no difference in the incidence of hypernatraemia between the two groups.[3] In our study, the mean sodium level was similar in the two groups. The LPN group, however, showed an increased incidence of hypernatraemia compared to the EPN group. NOHK is a common finding in VLBW neonates, occurring in 30–50% of babies during the first 72 hours of life.[18,19] A study of 62 extremely low birth weight (ELBW) babies demonstrated no difference in peak potassium and insulin levels during the first 3 days in the EHAA group compared to the SAA group.[13] Our study revealed that NOHK was significantly less in the EPN group.

OOP refers to the hypomineralised skeleton of the premature infant. The American Academy of Pediatrics recommends a minimum of 30–40 mg/kg of elemental calcium and phosphorus in TPN solutions for LBW infants, an amount well below the intrauterine accretion rate. The incidence of osteopenia was not significant in the two groups, but the need for phosphate supplementation was significantly less in the EPN group.

Cholestasis is a common complication of long term TPN in VLBW neonates.[20] In our study, the incidence of cholestasis was similar between the two groups. This may be explained by the fact that babies who received TPN for >4 weeks were excluded in both groups. The albumin levels in both groups did not show a difference, although studies by others have shown EPN to have a positive effect on albumin levels.[21]

There were various limitations of this study. First, there was the retrospective nature of the study with comparisons over 42 months. Second, there were no assessments of protein kinetics or body composition. More sophisticated measures of nitrogen balance and body composition are needed to define mechanisms of nutrient intake and growth in the preterm infant.

Conclusion

This study shows that EPN in VLBW babies is well tolerated. It appears to lead to a reduction in hypernatraemia, NOHK, OOP and the need for phosphate supplementation. Weight gain, time to regain birthweight, mean weight/day upto 34 wks CGA and time to full feeds showed no difference between the two study groups. Cholestasis and mean serum albumin levels showed no statistical difference between the groups.

CONFLICT OF INTEREST

The authors reported no conflict of interest and no funding has been received for this work.

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