THE EFFECT OF PARENTERAL NUTRITION WITH LIPOVENOUS OR INTRALIPID ON THE FATTY ACID COMPOSITION OF PLASMA AND ERYTHROCYTE MEMBRANE LIPIDS IN VERY-LOW-BIRTH-WEIGHT INFANTS

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The effect of two commercially available soya-oil emulsions, Lipovenous and Intralipid, on essential fatty acid status of plasma and erythrocyte membranes (EMB) in very-low-birth-weight (< 1 500 g) infants was investigated for 10% and 20% solutions, respectively ($N = 10$ for each group). Fat emulsions were infused for a period of 6 days at a rate of 1 g fat/kg/d from day 3 after birth, and increased by 0.5 - 1.0 g/kg/d to a maximum of 3 g/kg/d at day 9. The fatty acid response to total parenteral nutrition revealed no major differences between Lipovenous and Intralipid. The plasma phosphatidylcholine (PC) ω6/ω3 ratio increased less in the Intralipid group, mainly because docosahexaenoic acid (22:6ω3; DHA) decreased more after Lipovenous infusion, irrespective of the concentration of the lipid emulsions. Linoleic acid and α-linolenic acid present in the fat emulsions were incorporated into plasma and EMB PC, with concomitant decreases in their respective long-chain essential fatty acid metabolites, arachidonic acid (20:4ω6; AA) and DHA, irrespective of the type of lipid emulsion infused. The triene-tetraene ratio was significantly reduced after 6 days in plasma PC, but was not affected in the EMB lipids. Owing to the similarity between Lipovenous and Intralipid there is a pressing need to optimise the composition of these lipid emulsions so that the possible negative consequences of decreased AA and DHA during total parenteral nutrition can be prevented.

S Afr Med J 1999; **89:** 687-694.

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Preterm infants of very low birth weight (VLBW; < 1 500 g) are at risk of developing essential fatty acid (EFA) deficiency unless they receive an adequate supply of EFA.[1] These VLBW infants miss the period during pregnancy when long-chain polyunsaturated fatty acids undergo substantial accretion during the last trimester.[2] Premature infants have only limited linoleic acid (18:2ω6; LA) stores, which decline rapidly when they receive fat-free total parenteral nutrition (TPN) during the first 7 days after birth.[3] There are also indications that arachidonic acid (20:4ω6; AA) and docosahexaenoic acid (22:6ω3; DHA) are required for growth and development.[4] The rapid onset of EFA deficiency in VLBW infants on fat-free diets with only limited nutrient stores is therefore of great concern,[5] as an adequate supply of ω3 fatty acids plays an important role in early human visual acuity development.[6] The inclusion of only LA and α-linolenic acid (18:3ω3; ALA) in intravenous fat preparations[7] may be inadequate because VLBW infants are unable to compensate fully with new synthesis of AA and DHA from these C_{18} precursors.[5]

Children of mixed-race descent from local low socio-economic areas have a high prevalence (≈21%) of low birth weight (< 2 500 g),[8] with 4% being of VLBW.[9] Little information is available on the effect of TPN in VLBW infants with regard to fatty acid changes of tissue compartments such as erythrocyte membranes (EMB), or on the consequences of using TPN preparations with an unfavourable ω6/ω3 composition.[10] The fatty acid composition of EMB can be indicative of the fatty acid composition of the central nervous system during development, but plasma fatty acids respond more rapidly during short intervals.[11] None of the studies that investigated 10% and 20% fat emulsions have documented the effect on circulating fatty acids.[12,13] The intention of this study was to compare the effects of Lipovenous and Intralipid, each at both 10% and 20% solutions, on the plasma and EMB fatty acid status of VLBW infants who received TPN between 3 and 9 days of age.

MATERIALS AND METHODS

Patients

VLBW infants born at Tygerberg Hospital who required parenteral nutrition from day 3 of life were recruited from the neonatal intensive care unit to participate in the study, as described by Kirsten *et al.*[14] Exclusion criteria were congenital heart lesions and infections, chromosomal disorders, severe perinatal asphyxia, inborn errors of metabolism, infants of diabetic mothers, and jaundice requiring exchange transfusion. Neonatalyte (SABAX), a 10% dextrose/electrolyte solution, was provided intravenously to all infants during the first 2 days after birth. Fat, protein and dextrose solutions were administered according to routine procedures of the neonatal intensive care unit at Tygerberg Hospital.

Study design

The design was that of a double-blind randomised study. Forty VLBW infants were randomly assigned to four groups with 10 infants in each group. Groups received 10% Lipovenous, 10% Intralipid, 20% Lipovenous or 20% Intralipid, respectively, from day 3 of life. The study compared the effect of Lipovenous and Intralipid (at each concentration) on the EFA status of VLBW infants. The fat emulsions were prepared in the Admixture Unit and were randomised by a pharmacist. The bottles were then transferred to the neonatal intensive care unit with only the strengths of the emulsions known (10% and 20%). The code that revealed the brand name of the emulsions was only broken after the experiment was completed. The fat emulsions were infused through either a central or a peripheral vein over a 14 - 16-hour period each day, starting at a rate of ≈1 g/kg/d and increasing by 0.5 - 1.0 g/kg/d each successive day to a maximum of 3 g/kg/d on day 9. An amino acid/glucose solution containing 11 g glucose/100 ml was separately infused through a central vein and progressively increased over 4 days to reach a maximum concentration of 2.5 - 3.0 g protein/kg/d. The contribution of enteral nutrition (Prenan; Nestlé) to total energy intake was on average less than 10%. Blood glucose levels were maintained between 2 and 8 mmol/l. Total fluid intake was gradually increased from ≈60 ml/kg/d to ≈160 ml/kg/d over the first 7 days of life. Fluid intake was carefully monitored and adapted 12-hourly by the attending paediatrician when necessary. The study period was 6 days, which was preceded by a stabilisation period of 3 days. Gestational age was determined according to the new Ballard score[15] in conjunction with the mother's menstrual history. A birth weight below the 10th centile for gestational age was defined as growth retardation.[16]

Materials

Both soya-oil emulsions were analysed and demonstrated similar fatty acid compositions, except for DHA content (Table I). They differed only in that Lipovenous had a glycerol content of 25 g/l and fat particle size of 457 nm, compared with a glycerol content of 22.5 g/l and fat particle size of 397 nm for Intralipid.[3] The fat and glucose solutions were prepared under laminar flow in the hyperalimentation unit. Fat-soluble (Vitalipid) and water-soluble (Soluvit) vitamin preparations were also added to the soya-oil emulsions. Both TPN solutions were isonitrogenous and identical in nutrient composition. Each of these solutions was available as either 10% or 20% triglyceride emulsions and these differed in their phospholipid/triglyceride ratio (0.12 and 0.06, respectively).

Analytical methods

Blood samples were collected in EDTA tubes (1 ml) on day 3 before any lipid administration, and on day 9, 4 - 6 hours after the lipid infusion. EMBs were prepared by haemolysing

Table I. Composition of Lipovenous and Intralipid soya-oil emulsions (mean (SD))

	Lipovenous $N = 4$	Intralipid $N = 4$
Source	Soya oil	Soya oil
Egg phospholipid (%)	1.2	1.2
Glycerol (%)	2.5	2.25
Fatty acids* (%)		
14:0	0.12 (0.02)	0.16 (0.06)
16.0	10.79 (0.18)	10.16 (0.28)
16:1ω7	0.07 (0.01)	0.05 (0.02)
18:0	4.31 (0,06)	4.69 (0.04)
18:1ω9	23.33 (0.20)	22.58 (0.12)
18:2ω6	53.88 (0.22)	53.48 (0.35)
18:3ω3	7.01 (0.20)	7.85 (0.11)
20:2ω6	0.05 (0.00)	0.04 (0.00)
20:3ω6	0.01 (0.00)	0.01 (0.00)
20:4ω6	0.23 (0.01)	0.20 (0.11)
20:5ω3	0.01 (0.01)	0.00 (0.01)
22:4ω6	0.06 (0.00)	0.07 (0.04)
22:5ω3	0.01 (0.01)	0.01 (0.01)
22:6ω3	0.13 (0.01)	0.25 (0.01)
Particle size (nm)	457	397

*Own laboratory analysis.

erythrocytes with different phosphate buffers.[17,18] Owing to insufficient sample volume, only 7 of the 10% Lipovenous and 5 of the 10% Intralipid EMBs could be isolated (Table II). Lipids were extracted from plasma and EMB with chloroform/methanol (2:1; v/v), separated by thin-layer chromatography and analysed for fatty acid composition of plasma and EMB phosphatidylcholine (PC) by gas-liquid chromatography.[19,20]

Statistical analysis

All values are expressed as the mean and standard deviation (SD). Analysis of variance was used to compare birth weights, gestational ages, and energy and fat intakes between the four groups. Changes in each of the fatty acids from day 3 to day 9 were calculated. The significance of this change within each group was determined using the Wilcoxon signed rank test. The change obtained by either Lipovenous or Intralipid within either 10% or 20% solutions, respectively, was compared statistically by using the Wilcoxon two-sample test. This test was also used to compare the small-for-gestational-age (SGA) VLBW infants with appropriate-for-gestational-age (AGA) VLBW infants. Spearman correlations were done between LA intake and the change in plasma and EMB fatty acids,

Table II. The effect of Lipovenous and Intralipid on the percentage erythrocyte membrane PC fatty acid composition of VLBW infants before (day 3) and after (day 9) 10% TPN (mean (SD))

	Lipovenous ($N = 7$)		Intralipid ($N = 5$)		Lipovenous v. Intralipid (P-value)
	Day 3	Day 9	Day 3	Day 9	
∑SFA	47.14 (0.95)	44.56 (5.19)	47.82 (1.26)	45.98 (1.43)	-
16.0	25.90 (1.29)	26.77 (2.49)	26.14 (2.80)	25.54 (2.81)	-
18:0	20.94 (1.30)	17.55 (6.70)	21.33 (2.33)	20.32 (1.94)	-
∑MUFA	15.59 (1.71)	16.35 (1.95)	14.62 (1.24)	15.91 (0.50)	-
16:1ω7	1.32 (0.51)	0.60 (0.17)*	1.18 (0.44)	0.37 (0.10)	-
18:1ω9	14.26 (1.34)	15.73 (2.00)*	13.44 (0.94)	15.54 (0.53)	-
∑PUFA	37.27 (1.78)	39.11 (3.87)	37.56 (1.44)	38.11 (1.80)	-
18:2ω6	6.57 (1.35)	12.90 (1.70)*	6.48 (1.24)	13.96 (1.07)	-
18:3ω6	0.08 (0.04)	0.10 (0.07)	0.07 (0.05)	0.07 (0.04)	-
18:3ω3	0.02 (0.03)	0.21 (0.12)*	0.21 (0.20)	0.22 (0.15)	-
20:3ω9	1.76 (0.68)	1.48 (0.82)	0.79 (0.55)	0.97 (0.45)	-
20:3ω6	2.80 (0.33)	2.11 (0.44)*	2.99 (0.81)	2.19 (0.55)	-
20:4ω6	17.15 (1.77)	14.31 (2.40)*	17.60 (1.78)	12.63 (1.43)	-
20:5ω3	0.22 (0.10)	0.24 (0.06)	0.29 (0.14)	0.27 (0.03)	-
22:4ω6	2.10 (0.32)	1.64 (0.49)*	2.11 (0.33)	1.60 (0.36)	-
22:5ω3	0.70 (0.32)	0.68 (0.64)	0.21 (0.31)	0.39 (0.24)	-
22:6ω3	5.85 (0.81)	5.43 (1.26)	6.81 (1.26)	5.80 (0.95)	-
∑ω6	28.71 (1.64)	31.07 (3.44)	29.25 (1.80)	30.45 (1.54)	-
∑ω3	6.80 (0.90)	6.57 (1.17)	7.52 (1.15)	6.69 (1.11)	-
ω6/ω3	4.29 (0.62)	4.84 (0.86)	3.97 (0.72)	4.65 (0.84)	-
TTR	0.10 (0.05)	0.11 (0.06)	0.04 (0.03)	0.08 (0.04)	-

Statistical significance between day 3 and day 9 within each group: *$P < 0.05$.
TTR = triene/tetraene ratio (20:3ω9/20:4ω6).

irrespective of the type of soya-oil treatment. Probability values below 0.05 were considered statistically significant.

Ethical consideration

The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Stellenbosch and written informed consent was obtained from the parents before entry of infants into the study.

RESULTS

The clinical characteristics, energy, nitrogen, carbohydrate and lipid intake of the infants are shown in Table III. Birth weight and gestational age were similar in all groups, as were the fat intake (g/d), total energy, protein and carbohydrate intakes. Cholesterol and triacylglycerol profiles of these infants have been reported elsewhere.[14]

Tables II and IV - VI present the fatty acid composition of plasma PC and EMB PC in VLBW infants before (day 3) and after (day 9) 10% TPN and 20% TPN. Table IV shows that when Lipovenous was compared with Intralipid, the stearic acid (18:0; $P = 0.0257$) and ω6:ω3 ratio ($P = 0.0073$) increased, and DHA (22:6ω3; $P = 0.0211$) decreased significantly more in the 10% Lipovenous group. Within each group, irrespective of the type of lipid emulsion infused, plasma PC palmitic acid (16:0) and palmitoleic acid (16:1ω7) was decreased, while 18:0 was increased after infusion ($P < 0.01$). The plasma PC LA (18:2ω6) and ALA (18:3ω3) increased on both lipid emulsions, but their respective longer chain metabolites, namely dihomo-gamma linolenic acid (20:3ω6; DGLA) and AA (20:4ω6) and eicosapentaenoic acid (20:5ω3; EPA) decreased during 10% TPN ($P < 0.05$). DHA only decreased significantly ($P < 0.01$) during 10% Lipovenous infusion. Eicosatrienoic acid (20:3ω9; ETA; Mead acid; $P < 0.01$) decreased significantly and the total ω6 fatty acids increased significantly irrespective of the type of lipid emulsion. The total ω3 fatty acids decreased and the ω6/ω3 fatty acid ratio increased during 10% Lipovenous. The tetraene/triene ratio (20:3ω9/20:4ω6 ratio; TTR) decreased irrespective of the type of lipid emulsion during 10% TPN in the plasma PC ($P < 0.01$).

Table II presents the effect of 10% TPN on the EMB PC fatty acid composition. The only significant changes occurred in the group treated with the 10% Lipovenous. The 16:1ω7 decreased and 18:1ω9 increased significantly ($P < 0.05$). LA increased ($P < 0.05$), but the longer chain metabolites of LA, namely DGLA, docosatetraenoic acid (22:4ω6) and AA decreased significantly ($P < 0.05$). ALA was significantly increased after 10% Lipovenous in the EMB PC. Although the trend in changes during the 10% Intralipid infusion was similar, it was not significant owing to the small sample size.

Tables V and VI present the plasma PC and the EMB PC fatty acid composition, respectively, before and after 20% TPN. When comparing Lipovenous and Intralipid (Table V), plasma PC mono-unsaturated fatty acids (MUFA) ($P = 0.0247$) were more reduced in the Intralipid compared with the Lipovenous group owing to a reduction in oleic acid (18:1ω9; $P = 0.0247$) in the Intralipid group. DHA was also more reduced after 20% Lipovenous compared with 20% Intralipid, while the plasma PC ω6/ω3 ratio increased more during Lipovenous than Intralipid infusion ($P = 0.0373$). Within each group the plasma PC 16:0 ($P < 0.05$), LA ($P < 0.01$), total ω6 ($P < 0.05$) and the ω6/ω3 ratio ($P < 0.01$) increased, while DGLA, AA and DHA decreased ($P < 0.01$), irrespective of the type of lipid emulsion administered. Gamma-linolenic acid (18:3ω6; GLA) and ALA only increased significantly during 20% Lipovenous in the plasma PC. The total MUFA ($P < 0.01$) decreased during 20% Intralipid in the plasma PC owing to a significantly decreased oleic acid (18:1ω9; $P < 0.01$) concentration. This group also demonstrated a decreased TTR ($P < 0.05$) after infusion. Table VI shows that the only significant difference between

Table III. Clinical characteristics, energy, nitrogen, carbohydrate and lipid intake of VLBW infants receiving 10% and 20% Lipovenous or Intralipid parenteral nutrition treatments (mean (SD))

	10%		20%	
	Lipovenous ($N = 10$)	Intralipid ($N = 10$)	Lipovenous ($N = 9$)	Intralipid ($N = 10$)
Clinical characteristics				
Birth weight (g)	1 071 (141)	1 217 (190)	1 083 (211)	1 189 (211)
Gestational age (wks)	29.3 (2.5)	29.4 (2.0)	29.0 (1.0)	30.2 (1.7)
Parenteral intake (average for 6 days)				
Energy (kcal/d)	69 (12)	67 (14)	64 (13)	63 (6)
Fat emulsion (ml/d)	17.6 (4.6)	21.9 (4.9)	12.0 (3.2)	11.7 (2.8)
Fat (g/kg/d)	1.73 (0.44)	1.97 (0.60)	2.19 (0.46)	1.96 (0.28)
EFA intake (g/d)				
LA	0.93 (0.24)	1.06 (0.32)	1.18 (0.25)	1.06 (0.16)
ALA	0.14 (0.03)	0.16 (0.05)	0.17 (0.04)	0.16 (0.02)
Fat (g/d)	1.76 (0.44)	2.19 (0.49)	2.40 (0.63)	2.34 (0.56)

Table IV. The effect of Lipovenous and Intralipid on the percentage plasma PC fatty acid composition of VLBW infants before (day 3) and after (day 9) 10% TPN (mean (SD))

	Lipovenous ($N = 10$)		Intralipid ($N = 10$)		Lipovenous v. Intralipid (P-value)
	Day 3	Day 9	Day 3	Day 9	
∑SFA	43.85 (1.76)	43.45 (0.59)	43.71 (1.14)	43.51 (0.88)	-
16:0	31.57 (1.94)	28.75 (0.93)**	31.89 (1.39)	30.38 (0.73)**	-
18:0	12.28 (1.04)	14.70 (0.68)**	11.82 (0.88)	13.14 (0.71)**	0.0257
∑MUFA	23.50 (2.38)	22.10 (1.57)	23.96 (3.25)	23.33 (1.10)	-
16:1ω7	2.88 (0.70)	0.66 (0.22)**	2.91 (0.80)	0.77 (0.34)**	-
18:1ω9	20.62 (2.22)	21.44 (1.72)	21.04 (2.73)	22.55 (1.14)	-
∑PUFA	32.64 (2.31)	34.46 (1.55)	32.32 (2.73)	33.17 (1.68)	-
18:2ω6	7.46 (1.73)	20.21 (1.47)**	8.32 (1.95)	19.69 (2.39)**	-
18:3ω6	0.13 (0.06)	0.12 (0.05)	0.12 (0.03)	0.13 (0.09)	-
18:3ω3	0.07 (0.10)	0.27 (0.05)**	0.10 (0.11)	0.28 (0.06)*	-
20:3ω9	2.10 (0.94)	0.48 (0.30)**	1.72 (1.11)	0.31 (0.22)**	-
20:3ω6	2.74 (0.42)	1.23 (0.56)**	2.63 (0.80)	1.06 (0.66)**	-
20:4ω6	16.01 (2.26)	8.94 (2.14)**	14.71 (2.13)	7.35 (2.71)**	-
20:5ω3	0.41 (0.18)	0.25 (0.07)*	0.53 (0.22)	0.38 (0.10)*	-
22:5ω3	0.14 (0.10)	0.27 (0.08)*	0.24 (0.16)	0.22 (0.08)	-
22:6ω3	3.58 (0.76)	2.69 (0.50)**	3.94 (0.88)	3.75 (0.51)	0.0211
∑ω6	26.34 (2.64)	30.50 (1.62)**	25.78 (3.06)	28.23 (1.47)*	-
∑ω3	4.20 (0.87)	3.48 (0.52)*	4.81 (0.96)	4.63 (0.54)	-
ω6/ω3	6.49 (1.33)	8.94 (1.44)**	5.49 (1.00)	6.17 (0.80)	0.0073
TTR	0.14 (0.07)	0.05 (0.03)**	0.12 (0.08)	0.04 (0.02)**	-

Statistical significance between day 3 and day 9 within each group: *$P < 0.05$, **$P < 0.01$.
TTR = triene/tetraene ratio (20:3ω9/20:4ω6).

Lipovenous and Intralipid was ALA in the EMB PC, which increased more after 20% Lipovenous ($P = 0.0171$). Within the treatments, irrespective of type of emulsion infused, the changes in the EMB PC fatty acid composition were very similar to those obtained after 20% TPN in the plasma PC.

There were no significant differences in the fatty acid profiles between SGA and AGA infants at days 3 and 9 (results not shown). There was a significant negative correlation between LA intake and the change of AA in the EMB PC ($r = –0.42$; $P = 0.0159$) and DHA from day 3 to day 9 in the plasma PC ($r = –0.33$; $P = 0.0402$).

Discussion

This study describes and compares the effect of Lipovenous and Intralipid soya-oil emulsions at 10% and 20% concentrations respectively on fatty acid metabolism in plasma and EMB during TPN treatment of VLBW infants who were admitted to a neonatal intensive care unit within 3 days of birth. Irrespective of the concentration that was infused (10% or 20%), the response to either Lipovenous or Intralipid TPN revealed only minor differences in the plasma and EMB fatty acids. Kirsten *et al.*[14] reported significantly higher plasma cholesterol levels in infants who were treated with the 10% lipid emulsions, irrespective of the type of lipid emulsion. Despite the extensive use of TPN in neonates, currently administered fat emulsions may not be ideal in terms of promoting optimal growth and development of VLBW infants, as they lack adequate amounts of the long-chain EFA metabolites (AA and DHA) present in breast-milk.[21] Our study confirmed the findings of others[22-24] that LA and ALA are incorporated into the plasma and EMB PC after TPN. This incorporation is accompanied by concomitant decreases of their respective long-chain EFA metabolites, namely AA and DHA. In addition to comparing these two commercially available lipid emulsion preparations, this study also elaborates on the response of EFAs and their longer-chain metabolites in plasma and EMB over a relatively short period of 6 days.

The plasma PC fatty acid response to TPN demonstrated modest differences between Lipovenous and Intralipid. A statistically significant difference was observed in the plasma PC ω6/ω3 ratio, which increased less in the Intralipid groups, mainly because DHA decreased more after Lipovenous infusion in both the 10% and 20% groups. The higher DHA content of Intralipid compared with Lipovenous (0.25% v. 0.13%) may have contributed to the PC DHA of the group that

Table V. The effect of Lipovenous and Intralipid on the percentage plasma PC fatty acid composition of VLBW infants before (day 3) and after (day 9) 20% TPN (mean (SD))

	Lipovenous ($N = 10$)		Intralipid ($N = 10$)		Lipovenous v. Intralipid (P-value)
	Day 3	Day 9	Day 3	Day 9	
∑SFA	44.68 (1.72)	42.74 (1.55)*	44.02 (2.10)	43.66 (1.04)	-
16:0	30.81 (1.19)	26.90 (1.89)**	31.08 (2.16)	28.63 (1.71)*	-
18:0	13.87 (0.90)	15.84 (1.32)**	12.93 (1.22)	15.02 (1.41)*	-
∑MUFA	20.74 (4.47)	19.94 (1.18)	23.47 (3.67)	17.79 (1.36)**	0.0247
16:1ω7	2.09 (0.96)	0.55 (0.31)**	2.34 (0.70)	0.57 (0.37)**	-
18:1ω9	18.65 (3.80)	19.39 (1.11)	21.13 (3.16)	17.22 (1.31)**	0.0247
∑PUFA	34.58 (3.61)	37.32 (1.31)	32.51 (2.02)	38.55 (1.33)**	-
18:2ω6	9.48 (3.38)	23.04 (2.01)**	7.69 (1.82)	21.42 (2.76)**	-
18:3ω6	0.24 (0.14)	0.13 (0.10)*	0.09 (0.10)	0.10 (0.13)	0.0251
18:3ω3	0.06 (0.18)	0.26 (0.14)*	0.05 (0.12)	0.20 (0.13)	-
20:3ω9	1.81 (1.06)	0.61 (0.22)**	2.18 (1.17)	0.77 (0.31)**	-
20:3ω6	3.12 (0.72)	1.34 (0.26)**	3.02 (0.56)	1.94 (0.58)**	-
20:4ω6	15.81 (2.25)	9.41 (2.11)**	15.48 (1.82)	10.87 (1.75)**	-
20:5ω3	0.37 (0.25)	0.21 (0.09)	0.40 (0.31)	0.35 (0.15)	-
22.5ω3	0.07 (0.14)	0.18 (0.14)	0.10 (0.17)	0.22 (0.15)	-
22.6ω3	3.54 (0.33)	2.14 (0.33)**	3.48 (0.52)	2.68 (0.23)**	0.0199
∑ω6	28.72 (4.32)	33.92 (0.92)*	26.29 (2.52)	34.33 (1.52)**	-
∑ω3	4.05 (0.64)	2.79 (0.62)**	4.04 (0.73)	3.45 (0.45)	-
ω6/ω3	7.23 (1.45)	12.74 (3.03)**	6.69 (1.25)	10.14 (1.76)**	0.0373
TTR	0.12 (0.07)	0.06 (0.01)	0.14 (0.08)	0.07 (0.03)*	-

Statistical significance between day 3 and day 9 within each group: *$P < 0.05$, **$P < 0.01$.
TTR = triene/tetraene ratio (20:3ω9/20:4ω6).

received Intralipid being more resistant to a decrease of this fatty acid. Total MUFA in plasma PC, due to 18:1ω9, also decreased more after TPN in the 20% Intralipid group than in the Lipovenous group. The reason for this finding is not clear.

The reduced levels after TPN of AA and DHA in plasma and EMB PC are very important, because they indicate that tissue compartments are deprived of long-chain EFA metabolite accretion during this vital period of development in late pregnancy. VLBW infants are accordingly at risk of having lower circulating levels of AA and DHA than would be appropriate for their postnatal age.[25] The lower AA and DHA in the PC fractions could be the result of an increased demand for these fatty acids by VLBW infants, and/or an inability of the infant's enzyme systems to cope with the increased demand.

EFA deficiency is characterised by increased levels of ETA, and an increased TTR, which is the traditional marker for EFA deficiency.[26] Based on these criteria, 9 infants (23%) were biochemically EFA-deficient on day 3 because they had TTRs > 0.2.[14] ETA levels decreased significantly in plasma PC from day 3 to day 9 in both the 10% and 20% soya-oil emulsion groups, and in the EMB PC of the groups on the 20% soya-oil emulsion. TPN decreased the TTR levels to < 0.2 in plasma,[14] but had no effect on the TTR levels of the EMB over the 6-day period. This probably indicates that it may take much longer to reverse this biochemical marker of EFA deficiency to more favourable levels in tissues. Although ETA and TTR are indicative of EFA deficiency, these markers are not suitable in terms of indicating changes in the long-chain EFA metabolites AA and DHA.[27] Because the central nervous system actively incorporates AA and DHA during the growth spurt[2] that occurs from the 26th week of gestation until a few months after birth, a lowering of these fatty acids should be avoided in very preterm infants. Changes from this study could therefore mean that neural changes might persist[28] if over a short period of 6 days TPN fat emulsions are used over extended feeding periods in VLBW infants without adequate quantities of AA and DHA that resemble the composition of human milk.[29-31] Further investigations are therefore necessary in order to optimise the composition of TPN fat emulsions so that the important long-chain polyunsaturated fatty acids (LCPUFA) (e.g. AA and DHA) are not negatively affected.

The relatively strong negative correlation between LA intake and the change of AA and DHA levels in plasma and EMB provides ample evidence of the need to determine optimal concentrations and ratios of ω6 and ω3 EFA in TPN lipid emulsions in order to establish a fatty acid composition in the

Table VI. The effect of Lipovenous and Intralipid on the percentage erythrocyte membrane PC fatty acid composition of VLBW infants before (day 3) and after (day 9) 20% TPN (mean (SD))

	Lipovenous ($N = 10$)		Intralipid ($N = 10$)		Lipovenous v. Intralipid (P-value)
	Day 3	Day 9	Day 3	Day 9	
∑SFA	46.30 (1.00)	44.23 (0.85)**	46.66 (2.01)	44.33 (1.08)*	-
16:0	24:81 (1.11)	23.65 (1.17)**	24.90 (2.00)	22.97 (1.63)*	-
18:0	21.21 (0.88)	20.40 (0.72)	21.49 (0.93)	21.20 (1.01)	-
∑MUFA	15.86 (2.06)	15.65 (0.85)	15.69 (1.47)	15.48 (0.78)	-
16:1ω7	1.09 (0.57)	0.36 (0.10)**	1.42 (0.49)	0.43 (0.15)**	-
18:1ω9	14.77 (1.62)	15.29 (0.85)	14.27 (1.19)	15.05 (0.79)	-
∑PUFA	37.87 (1.57)	40.12 (1.28)**	37.64 (2.21)	40.19 (1.68)**	-
18:2ω6	6.79 (1.65)	14.50 (1.53)**	5.27 (2.07)	12.54 (1.57)**	-
18:3ω6	0.07 (0.04)	0.09 (0.01)	0.05 (0.04)	0.08 (0.07)	-
18:3ω3	0.07 (0.02)	0.24 (0.07)**	0.08 (0.06)	0.14 (0.10)	0.0171
20:3ω9	0.84 (0.28)	0.58 (0.33)*	1.06 (0.34)	0.87 (0.34)*	-
20:3ω6	3.17 (0.95)	2.37 (0.60)**	3.02 (0.49)	2.45 (0.42)**	-
20:4ω6	17.83 (1.52)	14.54 (1.23)**	18.75 (1.23)	15.74 (1.54)**	-
20.5ω3	0.25 (0.12)	0.24 (0.06)	0.27 (0.15)	0.27 (0.09)	-
22:4ω6	2.03 (0.34)	1.61 (0.23)**	2.02 (0.30)	1.77 (0.35)**	-
22:5ω3	0.54 (0.24)	0.72 (0.30)*	0.52 (0.33)	0.65 (0.32)	-
22:6ω3	6.08 (1.04)	5.22 (0.57)**	6.58 (1.02)	5.66 (0.72)*	-
∑ω6	30.08 (1.27)	33.12 (1.01)**	29.11 (1.59)	32.59 (0.84)**	-
∑ω3	6.95 (1.27)	6.42 (0.78)	7.46. (1.38)	6.73 (0.98)	-
ω6/ω3	4.45 (0.79)	5.23 (0.63)**	4.02 (0.75)	4.93 (0.67)**	-
TTR	0.05 (0.02)	0.04 (0.02)	0.06 (0.02)	0.05 (0.02)	-

Statistical significance between day 3 and day 9 within each group: *$P < 0.05$, ** $P < 0.01$.
TTR = triene/tetraene ratio (20:3ω9/20:4ω6).

infant that will ensure optimal growth and development. Indications are that both AA and DHA increase in brain phospholipids during prenatal development. These EFA long-chain metabolites should therefore be adequately included in fat emulsions[32] that are used for TPN of VLBW infants. This is further supported by the fatty acid composition of EMB which indicates that the fatty acid composition of the central nervous system may also be affected.[11]

Similar fatty acid profiles to those seen in VLBW infants fed human milk[33] are expected if preterm infants receive fat emulsions that contain a balanced composition of long-chain ω6 and ω3 fatty acids. Human milk from mothers who delivered preterm infants may, however, be inadequate to meet their infants' AA and DHA requirements.[34] Undeniable evidence indicates that the inclusion of long-chain ω3 fatty acids is essential, as DHA is an essential nutrient for normal eye and brain development to occur in VLBW infants.[35] The inclusion of adequate amounts of DHA into fat emulsions should therefore be seriously considered, as DHA deficiency has been shown to affect synaptic transmission during the critical period of brain development that might predispose to adult neurodegenerative disease.[36]

CONCLUSION

There were only small differences between the Lipovenous and Intralipid emulsions in this study. Whether Lipovenous or Intralipid emulsions are used is irrelevant as both products have nearly the same fatty acid composition, except for particle size and glycerol content. There is a pressing need to optimise the composition of these lipid emulsions so that the possible negative consequences of a decreased AA and DHA during TPN can be prevented. This will contribute towards a more optimal neurological development in those VLBW infants deprived of long-chain EFA metabolite accretion during the last trimester of pregnancy. The study elaborates on the rather rapid changes that were observed in EMB fatty acid compositions after the soya-oil emulsions were administered. However, the fatty acid results do not allow any conclusions to be drawn regarding the concentration of soya-oil emulsion (10% v. 20%) to be used. Consequently, more prospective clinical trials are needed to determine the long-term effects of TPN fat emulsions supplemented with long-chain ω3 and ω6 fatty acids on brain function of VLBW infants.

The authors wish to thank Mr Gert Engelbrecht, Miss Johanna van Wyk and Mrs Sheryl Kirsten for technical assistance, and Scotia Pharmaceuticals for financial support.

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Accepted 4 Apr 1998.