

Randomized Clinical Trial of Early Aggressive Versus Late and Slow Intravenous Lipid Infusion in Preterm Infants and Bilirubin and Lipid Profiles

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ABSTRACT

Objective: This study aimed to compare lipid profiles and total serum bilirubin of early aggressive versus late and slow intravenous fat emulsion infusion, in very-low-birth-weight premature infants over the first seven days of life.

Methods: A randomized, nonblinded and controlled trial that took place from January 2011 through June 2011 at the level III neonatal intensive care unit at Prince Hashem Bin Al-Hussein Hospital. Thirty low birth weight premature infants were randomized to three groups: Group A received Glucose 10% for the first 48 hours then 1g/kg/day Amino Acids and Intralipids and advanced by 1 g/kg/day on daily base to a total of 3.5g/kg/day and 3g/kg/day respectively. Group B received Glucose 10% and 1g/kg/day Amino Acids and Intralipids on day one and advanced by 1 g/kg/day, daily to a total of 3.5g/kg/day and 3g/kg/day respectively and Group C received Glucose 10%, 3.5g/kg/day Amino Acids and Intralipids 2g/kg/day started at birth then the intravenous intralipids advanced to 3g/kg/day on the next day. Serum levels of bilirubin, cholesterol and triglycerides were taken daily for all patients over the first seven days of life. Infants enrolled in this study had gestational ages between 28 and 32 weeks and had birth weights between 880 and 1500g. Infants who had serious congenital anomalies and/or developed early sepsis were excluded from participation. Data were analyzed using the Statistical Package for Social Sciences version 15. Repeated measures analysis of variance was used to test for the differences in the change of bilirubin, total cholesterol, and triglycerides over time and between groups A, B and C.

Results: The energy intake per day in group C remained statistically greater than that in group B and much greater than in group A for the first five days of the study period. There was no statistically significant difference in the mean fluid intake between the three groups. The mean fluid intake in all groups at seven days postnatal age was 162±8.5 ml/kg/day. During the study period, there were no clinically statistically significant differences in the mean serum cholesterol (102, 100, and 110 mg/dl), and mean serum triglyceride (92, 95.2, and 95.3 mg/dl), between group A, B, and C. The mean serum indirect bilirubin was greater in group C compared to group A and B (7.6, 5.74, and 7.14 mg/dl) but no clinical statistically difference between the three groups could be found. Levels of bilirubin, total cholesterol, and triglycerides increased linearly and significantly over the first seven days in all groups but did not rise to a serious level that needed intervention. The changes in these parameters were not different between the three groups.

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Conclusion: We conclude that early aggressive use of Intralipids (2g/kg/day immediately after birth) not only can be tolerated in low birth weight premature infants but also can significantly increase caloric intake that associated with no adverse effect on total serum bilirubin, total serum triglyceride and cholesterol concentrations. However, according to our study results there is no need for daily monitoring of total serum bilirubin and lipids profiles.

Key words: Amino Acids, Bilirubin, Cholesterol intralipids, Glucose.

Introduction

There is a marked increase in the number of very immature infants who can survive mainly due to advances in obstetrics and neonatal intensive care. Nutrition is becoming a key factor not only for the growth but also for life-long wellbeing of the premature infants.⁽¹⁾ Very-Low-Birth-Weight (VLBW) infants are born at a time of rapid intrauterine body and brain growth.⁽²⁾ The immature gastrointestinal tract of VLBW infants place them at risk for developing necrotizing enterocolitis (NEC). Traditionally, neonatologists began treatment with small amounts of macronutrients, such as Amino Acids at 0.5 g/kg per day and intravenous fat emulsion (IVFE) at 0.5 g/kg per day,⁽³⁾ because it was thought that larger amounts of IVFE would put the premature infants at increased risk for hyperlipidemia⁽⁴⁾ and hyperbilirubinemia.⁽⁵⁾ Many studies showed that provision of a large amount of Amino Acids (1.5–3 g/kg per day) from the first day of life was safe and can prevent protein losses.⁽⁶⁻⁸⁾ Intralipids are less studied due to many myths and dogmas.

The aim of this study is to compare lipid profiles and total serum bilirubin of early aggressive versus late and slow intravenous fat emulsion infusion in VLBW and to show that VLBW premature infants with birth weights of 880 to 1500g would be able to tolerate a higher IVFE infusion rate immediately after birth and during the first week of life (days 1–7), as could be demonstrated by maintenance of serum triglyceride levels of <200 mg/dl and also to

show that IVFE infusion is not associated with clinically significant higher levels of total serum bilirubin in VLBW premature infants.

Methods

A randomized, nonblinded and controlled trial that took place from January 2011 through June 2011 at the level III neonatal intensive care unit at Prince Hashem Bin Al-Hussein Hospital. A total of 30 sealed envelopes were used to facilitate the randomization of this trial.

Ten sealed envelopes indicated that the infant would be assigned to group A, 10 sealed envelopes indicated that the infant would be assigned to group B, and 10 envelopes indicated that the infant would be assigned to group C. Infants who were enrolled in this study had gestational ages between 28 and 32 weeks and had birth weights between 880 and 1500g. Infants who were small for gestational age at birth, had serious congenital anomalies, and/or developed early sepsis were excluded from participation in the study. Infants in group A began treatment with Glucose 10% for the first 48 hours then 1g/kg/day Amino Acids and 20% Intralipids started and advanced by 1g/kg/day to total 3.5g/kg/day and 3g/kg/day respectively. Infants in group B began treatment with Glucose 10%, 1g/kg/day Amino Acids and 20% Intralipids started on day one and advanced by 1g/kg/day to total 3.5g/kg/day and 3g/kg/day respectively. And infants in group C began treatment with Glucose 10%, 3.5g/kg/day Amino Acids and 2g/kg/day 20% Intralipids advanced to 3g/kg/day on next day since first day of life. The intravenous fat emulsion was administered covered from light in a glass bottle through an umbilical venous catheter continuously over 20 hours. Data collection was completed by a neonatologist in the NICU. The following information were collected: demographic data, birth weight, gestational age at birth, serum triglyceride, cholesterol, liver enzyme and total serum bilirubin levels and other nutritional laboratory values during the first seven days of TPN. The neonatologist calculated the total kilocalories per kilogram per day. Ethical approval was taken from JRMS ethical committee.

Table I: Neonatal demographic data of the study group

	Group A	Group B	Group C
GA (week)	30±2	30±2	30±2
BWT(Kg)	1.35	1.42	1.4
GENDER (M:F)	4:4	6:4	5:4
Apgar score at 5min	8±1	8±1	8±1

Table II: Mean caloric intake (Kcal/Kg/d) among the study group

	Group A	Group B	Group C
Day 1	28±1.5	40±1.3	52±1.2
Day 2	36.7±2.3	58.6±1.5	73.2±1.2
Day 3	57.5±2.5	77.9±2.4	79.4±2.7
Day 4	76.6±3.6	85.2±2.8	88.2±3.3
Day 5	96.3±4	95.5±3.5	97.2±3.8
Day 6	108.6±5.2	107.9±4.2	107.5±5.1
Day 7	121.8±6.3	120.8±4.7	122±4.9

Table III: Mean laboratory values for the three study groups

	Group A				Group B				Group C			
	BUN*	CREAT*	TG*	CHOL*	BUN	CREAT	TG	CHOL	BUN	CREAT	TG	CHOL
Day1	8±6	0.7±0.3	73.6±13.6	79.1±11.3	12±5	0.7±0.3	85±16.4	78.6±18.2	7±5	0.6±0.3	76.3±15.3	85.7±19.7
Day2	9±8	0.6±0.3	76.7±12.2	80.6±17.6	9±5	0.7±0.4	84.4±17.3	86.3±23.4	8±6	0.5±0.3	88.7±21.4	96.6±18.5
Day3	8±8	0.6±0.2	84.1±14.1	86.7±18.4	7±5	0.5±0.4	87.8±13.9	90.5±27.5	7±5	0.5±0.4	77.6±18.5	111.6±16.7
Day4	11±7	0.5±0.3	92 ±12.3	103.1±22.4	7±4	0.4±0.3	112.5±21.1	98.5±19.9	6±4	0.5±0.4	91.6±21.3	110.3±25.3
Day5	6±5	0.4±0.3	99.2±15	120.7±26.3	6±5	0.3±0.2	94.1±18.5	114.8±25	5±4	0.4±0.3	96.6±15.8	118.2±28.4
Day6	7±5	0.4±0.3	107±16.3	120.1±28	7±4	0.4±0.3	98.8±19.5	116.1±26.4	7±3	0.3±0.2	122.3±22.7	125.9±30.3
Day7	7±5	0.4±0.3	112±14.2	128±23.7	6±4	0.4±0.2	104±17.9	120±19.6	6±3	0.4±0.2	114.4±18.6	127.6±22.9

*mg/dl

Table IV: Mean laboratory values for the three study group

	Group A				Group B				Group C			
	GLU*	Bilirubin*	ALT**	AST**	GLU	Bilirubin	ALT	AST	GLU	Bilirubin	ALT	AST
Day 1	70	0.5	10	19	60	2	7	18	65	1.5	11	18
Day 2	80	4	9.2	20	70	5	8	17	68	5	8.3	20
Day 3	75	7	8	20.7	80	8	7	19	73	8	9	21
Day 4	76	7	10.6	20	81	9	6	18	76	9	11	19
Day 5	81	6.3	7.1	23	73	10	8	19	69	9	7	22
Day 6	82	7.1	7.2	25	75	9	8	18	70	11	8	23
Day 7	88	8.3	8.5	20	77	7	8	23	76	10	7	19

*mg/dl **U/L

Results

Thirty infants were eligible to be enrolled in this study. Three infants were withdrawn from the study because of exclusion criteria being met and/or deviations from the study protocol.

Of the 27 infants who completed the study, 8 infants were in group A, 10 in group B and nine infants were in group C. There were no significant differences in race, gender, gestational age, birth weight or in five minutes Apgar score between the groups, (Table I). The energy intake per day in group C remained statistically greater than that in group B and much greater than in group A for the first five days of the study period, as shown in Table II. There was no difference in the mean fluid intake between the three groups. The mean fluid intake in all groups

at 7-days postnatal age was 162±8.5 ml/kg/day. During the study period there were no clinically significant differences in the mean serum cholesterol (102, 100, and 110 mg/dl), and the mean serum triglyceride (92, 95.2, and 95.3mg/dl) between group A, B, and C, (Table III). The mean serum indirect bilirubin was greater in group C compared to group A and B (7.6, 5.74, and 7.14 mg/dl), as illustrated in Table IV. But no clinical difference between the three groups could be found. During the 7-day study period mean serum Glucose concentration was higher in the group A compared to group B and C. Repeated measures analysis showed the levels of bilirubin, total cholesterol, and triglycerides increased linearly and significantly over the first seven days in all groups (Table III, IV). The

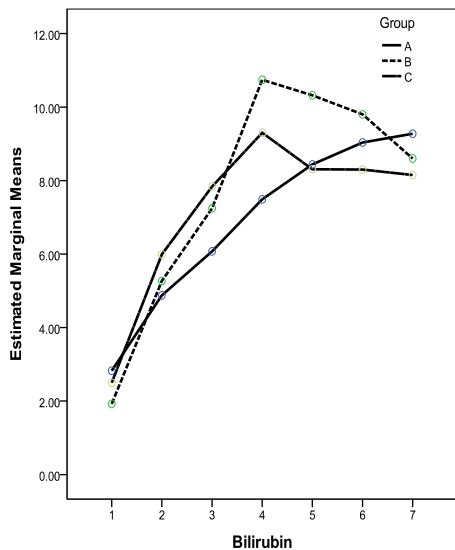


Fig. 1: Shows the linear increase of mean total serum bilirubin levels over the first seven days of life in all three groups.

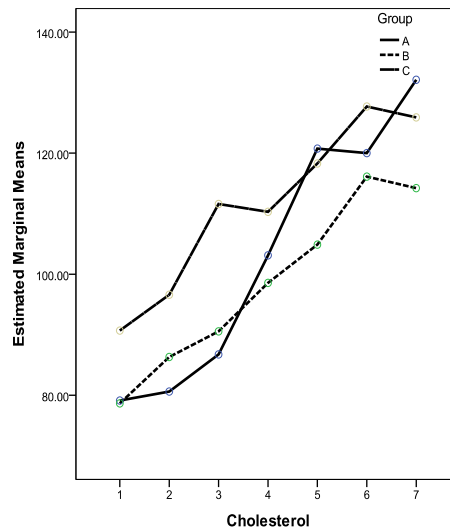


Fig. 2: Shows the linear increase of mean serum cholesterol levels over the first seven days of life in all three groups.

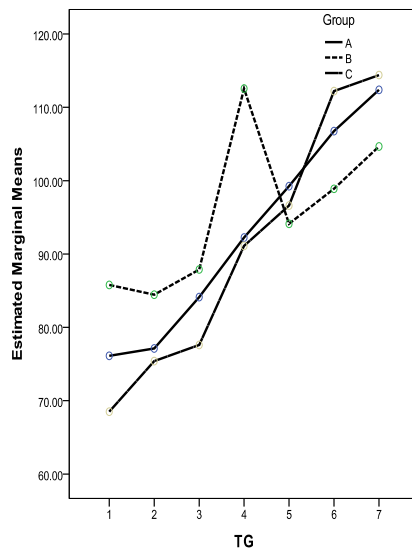


Fig. 3: Shows the linear increase of mean serum triglyceride levels over the first seven days of life in all three groups.

changes in these parameters were not different between the three groups. Furthermore, there was no significant interaction between the group and time effects. The changes in these parameters are shown in Figures 1, 2, and 3.

There was no intervention related mortality among the three groups. One infant in group A died at day 14 due to intestinal obstruction and two infants (one in group A and the second one in group B) developed klebsiella sepsis. There were no differences in the secondary outcomes (BPD, IVH, and PDA).

Discussion

We are trying to introduce a new approach to parenteral feeding in VLBW infants in Jordan. Our article is at least the first one in Jordan and the region. Two randomized control trials assessing the effect of infusion of high dose IVFE (2-3 g/kg/d) to neonates especially VLBW and ELBW infants from the first day of life on various outcomes were identified in the literature: Ibrahim *et al.*⁽²⁾ and Drenckpohl *et al.*⁽⁹⁾ Still there is no agreement on the ideal age at which to introduce intravenous Amino Acids (AA) and

Intralipids (IL) to the feeding of a VLBW premature infants.^(10,11) In Jordan, a great number of neonatologist prefer not to use intravenous Intralipids at all and many NICUs both in Jordan and all over the world if they use IVFE they start it after several days of birth (48-72 hrs) with starting dose 0.5-1g/kg/d, then advance very slowly: 0.5, 1.0, etc. every few days due to many myths and dogmas that surround IVFE such as increase risk of sepsis, bilirubin-albumin displacement, hyperlipidemia, increase mortality rate, increase the incidence of BPD and other complications. But we think that this approach is based on tradition rather than science. It is well known that ELBW preterm infants are vulnerable to insufficient lipid supply because significant in utero fat accretion does not occur until the third trimester.⁽¹²⁾ As the accretion of adipose tissue begins at gestational age of 25 weeks and continues at 1-3 g/kg/day.⁽¹³⁾ Fetal energy metabolism is not dependent on fat until the third trimester, and it then increases gradually toward term. The fetus depends mainly on placental transfer of essential fatty acids (EFA).⁽¹⁴⁾ And to prevent fatty acid deficiency an intake of linoleic acid and linolenic should be at 4 - 5% and 1% of total calories respectively.^(15,16) Essential fatty acids deficiency may be present at birth in VLBW premature infants, but mostly can develop over 72 hours of deprivation⁽¹⁷⁻¹⁹⁾.

In our study, no single premature infant showed any sign of essential fatty acid deficiency (EFAD) because IVFE was started in all groups before the age of 72 hours. ELBW infant with deficient dietary intake, needs to mobilize fatty acids very early for caloric needs. By simple calculations (assume 1 kg premature infant):- Need total of 80 Kcal/kg/d for growth: Glucose: 8 mg/kg/min \approx 39 Kcal, Amino Acids: 3 g/kg/d = 12 Kcal, Still need \approx 30 Kcal from lipids: (30Kcal X cc /2.2 Kcal) X 0.2 g/cc = 2.7 g/d. Our study showed that the energy intake per day in group C in which we used 2g/kg/day from day one remained statistically greater than that in group B and much greater than in group A for the first five days of the study period. Our new approach by increasing caloric intake by providing high dose of IVFE proved to be successful and not by increasing the infusion rates of glucose greater than 12 mg/kg/min which may exceed capacity for infants with respiratory

problems to eliminate CO₂ because of high respiratory quotient of glucose which can put the premature infant who is already susceptible for hyperglycemia in real great risk. The clearance of lipid infusions is based on both: the rate and the interval of infusion.⁽²⁰⁾ In our study, we used a rate of 0.15g/kg/hour of IVFE over 20 hours continuous infusion like many other studies that showed that rate not exceeding 0.25 g/kg/h over 24 hours in full term infant and 0.15 g/kg/h over 24 hours in VLBW infants is well tolerated and associated with no increase in plasma lipid values.^(2,9,12,21-23) A study by Adamkin *et al.*⁽²⁴⁾ showed that premature infants who receive continuous infusions of IVFE over 20-24 hours period could tolerate serum triglyceride levels of < 250 mg/dl without any consequences. In our study we used the 20% lipids because it has been proved that Lipids of 20% has half amount of phospholipids relative to the same amount of triglycerides that making it had a more efficient clearance of triglycerides even at higher infusion rates than 10% solution. In our study we delivered the 20% lipids from glass bottles covered from light because a retrospective study by Martin *et al.*⁽²⁵⁾ showed that patients who are receiving lipids delivered in plastic bags are more likely to have hypertriglyceridemia than those who are receiving lipids from glass bottles. Our study showed that there is no need for the incremental increase in intravenous lipid infusion because there is no clinical evidence to support the common practice of gradually increasing the daily lipid intake to induce more lipid clearance.⁽¹²⁾ Research indicates using a high starting dose 2 to 4g/kg/d of intravenous lipids in newborn (term, VLBW and ELBW) infants^(2,9,21-23) showed that these doses are well tolerated with no significant increase in serum total triglycerides and stepwise increase in intravenous lipid infusion in VLBW and ELBW infants does not improve the clearance or tolerance of lipids. Results in our study showed that there were no significant differences in the mean serum cholesterol and triglyceride between the three groups during the study period.

Most premature infants with low birth weights develop clinically significant hyperbilirubinemia (jaundice) that requires intervention and they are at higher risk for kernicterus at levels of total serum bilirubin far below those in more mature

infants. There is clear evidence that intravenous lipid emulsion do not have a significant effect on indirect hyperbilirubinemia in both VLBW and ELBW infants.^(2,5,21,24) Several studies using a high starting dose 3 to 4 g/kg/d of intravenous lipids in newly born VLBW and ELBW infants^(2,21,24) showed that high dose (3 to 4 g/kg/d) immediately after birth can be tolerated in VLBW and ELBW infants with no adverse effect on total serum bilirubin concentration. Our study supported these results as data in our study showed that the mean serum indirect bilirubin was greater in group (C) compared to group A and B (7.6, 5.74, and 7.14mg/dl) (Table IV). But there was no clinical difference between the three groups found. According to our results we suggest that there is no need for daily bilirubin and lipid profile monitoring and twice or even once weekly monitoring or as clinically indicated is fair enough.

In summary, many of the dogmas that have prevented early use of intravenous lipids have either been disproved, not based on fact or are weak. There are compelling reasons for early use of high dose (2g/kg/day) intravenous lipids which include prevention of EFA deficiency, and provision of energy. Even our study showed that early aggressive use of Intralipids in low birth weight premature infants can significantly increase caloric intake with no adverse effect on bilirubin, triglyceride and cholesterol concentrations. However, many questions remain about other side effects of intravenous Intralipids infusion and need further evaluation.

Limitation of the Study

Further studies with larger number of low-birth weight premature infants are needed.

Conclusion

We conclude that early aggressive use of Intralipids (2 g/kg/day immediately after birth) not only can be tolerated in low birth weight premature infants but also can significantly increase caloric intake with no adverse effect on total serum bilirubin, total serum triglyceride and cholesterol concentrations. However, according to our study results there is no need for daily monitoring the total serum bilirubin and lipids profiles.

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