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Original Article

Evaluating the effects of two different lipid emulsions on morbidities in premature infants

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Abstract

Aim: The aim of this study is to evaluate the effect of OO and FO based LEs on morbidities in preterm infants.

Materials and Methods: A total of 44 neonates with a gestation ≤32 weeks were included in this retrospective observational study. The study group composed of neonates (n=28) who received SMOFlipid and the control group consisted of infants (n=16) who received ClinOleic. Demographic and clinical data of the neonates in terms of duration of PN, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD),), duration of mechanical ventilation (MV), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), PN-associated cholestasis (PNAC) and plasma triglyceride (TG) levels (mg/dl) were collected and compared statistically.

Results: We did not find significant difference in terms of RDS, BPD, NEC, IVH, ROP and PNAC. The study group had lower TG levels than the control group which were 93.03±24.55 mg/dL and 151.31±114 mg/dL, respectively (p=0.002).

Conclusion: Both LEs are well tolerated and safe without any side effects in preterm infants. Although both LEs have no significant effect on morbidities, FO based LE provide better TG levels than OO based LEs.

Keywords: Hypertriglyceridemia; lipid emulsion; morbidities; preterm infants

INTRODUCTION

In the last decades, in the era of advances in perinatal medicine and sophisticated improvements in neonatology, the survival rates of preterm and very low birth weight infants increased. Owing to necrotizing enterocolitis (NEC) and feeding intolerance, postnatal growth restriction is an important problem in this vulnerable group of infants (1). It is crucial to provide optimal growth and development during the transition to enteral feeding in the first weeks of life. Therefore, parenteral nutrition (PN) became the standard treatment for these neonates (2,3). Lipid emulsion (LE) is the significant component of PN which is the source of essential fatty acids (EFAs) which cannot be synthesized by humans and must be provided in the diet and supplies energy to the neonate (4,5).

Content of the LEs is important particularly for the developing brain and retina (3,6,7). These emulsions are the source of EFAs and long-chain polyunsaturated fatty acids (PUFA) which are extremely limited synthesized by the preterm infants (7). Moreover, LEs affect the immune system via phagocytosis, cell membrane properties, and production of bioactive molecules (8,9). The widely used LEs are based on soybean oil (SO) however in the recent year's olive oil (OO) or fish oil (FO) based LEs have been used instead.

SO contains omega-6 PUFAs such as linoleic acid and has a potential to increase inflammation and lipid peroxidation. ClinOleic which is an OO based LE (80% OO, 20% SO) is rich in monounsaturated fatty acids (MUFAs), has low levels of omega-3 PUFAs and higher omega-6:omega-3 ratio. SMOFlipid which is a mixture of different types of oils (20% OO, 30% SO, 30% coconut oil, 15% FO) is rich in EFAs, MUFAs, omega-3 fatty acids besides contains antioxidant α-tocopherol and has a lower omega-6:omega-3 ratio (5,10-13). Due to its content, it contributes to the neurodevelopment, vision and immune activity of the neonate especially by reducing oxidative stress and lipid peroxidation (5). FO based LEs may decrease the incidence of morbidities related to oxidative stress by reducing lipid peroxidation. This study was designed to compare OO and FO based LEs and evaluates the impact of these two LEs on morbidities in preterm infants.

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MATERIALS and METHODS

Study Design

This retrospective observational study was performed in level III NICU of Umraniye Training and Research Hospital, between January 2014 and January 2015. Umraniye Training Hospital is a tertiary hospital with 24 incubators and approximately 500-600 annual admissions. The study was executed in accordance with the Declaration of Helsinki, and approved by the ethics committee of the same hospital (approval number 9549/19.06.2015). There was no funding source relevant to the study.

According to the medical reports, during the study period 437 infants were hospitalized. Of 57 inborn infants, 4 infants with congenital malformations, 2 infants with chorioamnionitis, 3 infants with culture proven sepsis, 1 infant who had asphyxia, 1 infant with indirect hyperbilirubinemia requiring exchange transfusion, 1 infant with metabolic disorder and bleeding disorder were excluded from the study. A total of 44 patients with a gestation ≤32 weeks were included in the study.

During the study period, 2 brands of lipid solutions were used in our NICU: until May 2014, ClinOleic (20%; Baxter S.A., Lessines, Belgium) was routinely used and the infants who received ClinOleic until this time were recruited into group 1 (control group, n=16). After May 2014, SMOFlipid (20%; Fresenius Kabi, Mount Kuring-Gai, NSW, Australia) was used and infants who received SMOFlipid after this time were included in group 2 (study group, n=28).

According to our unit policy, PN was initiated with intravenous (IV) glucose and amino acid solution in the first hours of life. The IV glucose was started with 4-6 mg/kg/min and gradually increased to 10-12 mg/kg/min with respect to blood glucose level. Amino acids were derived from Primene (Eczacibasi-Baxter, Istanbul) which was commenced at 2 g/kg and every 24 hour it was increased by 1 g/kg until reached to a maximum of 4 g/kg/day. LE was started on second day of life with the initial dose of 1 g/kg/day and every 24 hour it was increased by 1 g/kg/day until a maximum of 3 g/kg/day as a continuous infusion for 18 hour per day. As the lipid intake was reached to 3 g/kg/day, plasma triglyceride (TG) concentrations were measured and then checked for weekly. The goal was to maintain triglyceride levels below 200 mg/dL. Enteral feeding was started in the first hours of life with a volume of 10-20 mL/kg/day divided into doses given every two to three hours. The infants were fed either with breast milk or premature infant formula. According to the infant's tolerance, the intake was increased by 10-20 mL/kg/day until reaching to full enteral feeding (120-160 ml/kg/day). LE infusions and PN were reduced gradually and ceased when the infant's enteral feeding volume reached over 100 ml/kg/day. Therewithal, breast milk was fortified with human milk fortifier after PN was ceased.

Demographic and clinical data about neonates were collected in terms of birth weight (BW), gestational age (GA), gender, time of full enteral feeding (day), duration of PN (day), respiratory distress syndrome (RDS), oxygen need, duration of mechanical ventilation (MV), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), PN-associated cholestasis (PNAC), duration of hospitalization, mortality and plasma TG levels (mg/dl).

The GA of the neonates was based on dating ultrasound performed in the first trimester of pregnancy in addition to the date of the last menstrual period of the mother. RDS was defined as having respiratory distress with the characteristic radiological findings (14). BPD was defined as the preterm infants receiving oxygen therapy or assisted ventilation at postnatal 28th day (15). PDA was diagnosed according to transthoracic echocardiography performed by the pediatric cardiologist (16). IVH was diagnosed by cranial ultrasound and classified according to Papile grading system (17). NEC was diagnosed and managed with respect to Bell's staging criteria (18). ROP Screening examinations were performed in accordance with the follow-up schedule recommended by the American Academy of Pediatrics and American Academy of Ophthalmology (19). Cholestasis was defined as direct bilirubin > 1 mg/dL when the total bilirubin is <5 mg/dL, or as direct bilirubin > 20% of the total bilirubin when total bilirubin is ≥5 mg/Dl (20).

Statistical Analysis

We used the SPSS software for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA) for statistical analyses. The variables were investigated using visual (histograms, probability plots) and analytical methods (Shapiro-Wilk test) to determine if they are normally distributed. Descriptive analyses were presented using means±SD for normally distributed variables, as medians (range, 25–75%) for the nonparametric variables and as percentages for categorical variables. Normally distributed variables were compared by Student t-test, nonparametric variables by Mann–Whitney U test, and categorical variables by chi-square test. Incidence rate comparisons using two-sided mid-P exact test have been performed with Stata/MP 13.1. Poisson exact confidence intervals were presented for incidence rates. $P < 0.05$ was considered to indicate a significant difference.

RESULTS

A total of 44 infants were eligible for the study. Twenty-eight infants received SMOFlipid (study group) and 16 received ClinOleic (control group). In the study group there was preponderance of females over males however, in the control group the number of male and female subjects were equal and it was not statistically significant (p= 0.2). The lowest GA was 23 weeks. The mean GA in the study and control group were 28.9±2.2 weeks and 28.9±1.9, respectively (p=0.86). The lowest BW was 510 grams whereas the highest BW was 1890 grams. There was no statistically significant difference between the groups in terms of clinical characteristics except for plasma TG levels (Table 1). Plasma TG levels were 93.03±24.55 mg/dL and 151.31±114 mg/dL in the study and the control groups, respectively (p=0.002). One infant from each group died which was not statistically significant.

Table 1. Characteristics of the infants

Parameters	Study group (n= 28)	Control group (n=16)	p value
GA (weeks), (mean±SD)	28.9 ± 2.2	28.9 ± 1.9	0.86
BW (g), (mean±SD)	1118 ± 271	1042 ± 239	0.39
Gender (girl), n (%)	20 (71)	8 (50)	0.2
BPD, n (%)	10 (35.5)	6 (37.5)	0.35
ROP, n (%)	10 (35.5)	7 (43.8)	0.59
Oxygen need (day), (mean±SD)	27.46 ± 29.8	18.06 ± 20.9	0.14
Time of full enteral feeding (day), (mean±SD)	18.07 ± 8.97	19.81 ± 10.94	0.60
Duration of MV (day), median (25-75 p)	6.5 (2.2-27.25)	5.5 (3-13.75)	0.45
Duration of PN (day), median (25-75 p)	18.1 (12-22)	20.4 (12.3-24.3)	0.79
Triglyceride level (mg/dL), (mean±SD)	93.03 ± 24.55	151.31 ± 114	0.002
IVH, n (%)	3 (18.8)	4 (14.2)	0.8
Cholestasis, n (%)	2 (7.1)	4 (25)	0.17
RDS, n (%)	21 (75)	12 (75)	0.6
NEC, n (%)	1 (3.6)	1 (6.3)	1
PDA, n (%)	13 (46.4)	9 (56.2)	0.15
Mortality, n (%)	1 (6.3)	1 (3.6)	1
Duration of hospitalisation, median (25-75 p)	50 (30.5-72.75)	48 (29-61)	0.66

BW: birth weight, GA: gestational age, PN: parenteral nutrition, RDS: respiratory distress syndrome, MV: mechanical ventilation, BPD: bronchopulmonary dysplasia, PDA: patent ductus arteriosus, NEC: necrotizing enterocolitis, IVH: intraventricular hemorrhage, ROP: retinopathy of prematurity, PNAC: parenteral nutrition associated cholestasis (PNAC), TG: triglyceride

DISCUSSION

In the present study, both LEs were found to be well tolerated and safe without any side effects in preterm infants. We demonstrated that the infants who received FO based LE had a lower risk of hypertriglyceridemia than the ones who received OO based LE. On the other hand, there was no statistically significant difference in terms of RDS, BPD, NEC, PDA, IVH, ROP, mortality and PNAC.

In preterm neonates especially in sick infants, enteral feeding is difficult and occurrence of feeding intolerance or NEC may cause the feeding to fail. Thus, PN becomes the main method to provide nutritional support to these infants (1,21,22). On the other hand, long term use of PN is associated with complications including catheter-related infections, hypertriglyceridemia or cholestasis (23). Apart from such complications, the major goal of PN should be providing proper development of the vital organs of the infants in order to prevent long term complications. LE is one of the main components of PN. Although the superiority of LEs is not clear enough to establish a general consensus, the most widely used LE is SO based ones. In the recent years, the concerns about its excess PUFA and low vitamin E content, the clinicians searched for different types of LEs. OO based LEs contain more amount of MUFAs, vitamin E and lower PUFAs than SO based LEs. On the other hand, FO based LEs is rich in omega-3 fatty acid and vitamin E than OO based LEs.

It has been suggested that LEs containing FO decreases oxidative damage. Oxidative stress is the result of the imbalance of free radical production and the anti-oxidative capacity. It begins before birth and it is high in preterm infants. The complications of prematurity such as BPD, NEC, IVH and ROP are thought to be related with oxidative damage (2,24). Deshpande et al. (5) evaluated thirty preterm neonates who received SMOFlipid and ClinOleic reported that SMOFlipid showed beneficial effects in terms of reduction of oxidative stress. Ozkan et al. (3) conducted a prospective randomized study with 89 preterm infants whose GA is below 32 weeks and compared the oxidative stress associated morbidity between infants using SMOFlipid and ClinOleic. They concluded that SMOFlipid can decrease the prevalence of BPD. Another study done with 227 infants whose GA were between 25 and 32 weeks comparing oxidative stress and morbidities of infants receiving SMOFlipid and ClinOleic demonstrated that, there were statistically insignificantly higher rates of BPD and ROP in infants receiving ClinOleic with no statistically significant differences in morbidity rates between the groups (2). The results of the present study showed that important clinical morbidities of preterm infants including RDS, NEC, IVH, BPD and ROP did not differ by the type of LE used.

Initiating LEs soon after birth is safe with considerable benefits including improved nitrogen balance and growth plus better control of hyperglycemia (25). For both term and preterm infants receiving LEs, ESPGHAN 2005 Guidelines recommend to monitor and suggest a plasma triglyceride level of 250 mg/dL (2.8 mmol/L) (26). Hypertriglyceridemia is a metabolic complication often occurring in preterm infants receiving PN due to the limited muscle and fat mass (27). Although monitoring of plasma

TG is recommended, the higher levels may decrease LE intake and result in a lower energy intake. Sinclair et al. (28) conducted a study with 195 infants <29 weeks gestation receiving SMOFlipid and ClinOleic. Although they did not mention the content of the LE, they reported that hypertriglyceridemia was associated with severe ROP and an increase in mortality in preterm infants. In contrast, Holtrop et al. (29) showed that TG levels >200 mg/dl did not predict future mortality or morbidity in extremely low birth weight infants receiving SO LEs. In the present study, although there was no difference between two groups in terms of complications due to prematurity, we found that hypertriglyceridemia was less in SMOFlipid group.

Infants on prolonged PN, PN-associated cholestasis (PNAC) become a risk in preterm infants. Although the exact pathogenesis of PNAC is not known, prematurity, small for gestational age, longer duration of PN, NEC, delay in enteral feeding and content of the PN solutions are thought to be the possible causes (1,30). The recent studies demonstrate that FO based LEs have a preventive effect on PNAC (31-33). However, Lee et al. (1) conducted a study with 114 preterm infants diagnosed with PNAC and did not observe the protective effect of FO based LE against PNAC. In our study, 2 infants receiving SMOFlipid and 4 infants receiving ClinOleic developed PNAC which was not statistically significant.

LIMITATIONS

This study has some limitations. First, it is a retrospective study and it compares two different LEs in two different time periods without any randomization. Another limitation is the small sample size. The last limitation is that we did not use any marker for the prediction of in vivo oxidative stress such as plasma F_2-isoprostanes or anti- and pro-inflammatory cytokines (IL-6, IL-10, and IL-1B).

CONCLUSION

In conclusion, we observed that both SMOFlipid and ClinOleic are well tolerated and safe in preterm infants. Although we did not find significant difference in terms of RDS, BPD, NEC, IVH, ROP and cholestasis, the risk of hypertriglyceridemia was lower in infants who received SMOFlipid. Further studies with larger sample sizes are required to compare different contents of LEs and moreover to investigate the long-term outcomes of LEs.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: Umraniye Training and Research Hospital Ethical Committe decision number: 9549, date: 19.6.2015.

REFERENCES

1. Lee HH, Jung JM, Nam SH, et al. Risk factor analysis of parenteral nutrition-associated cholestasis in extremely low birth weight infants. Acta Paediatr 2016;105:313-9.
2. Unal S, Demirel N, Erol S, et al. Effects of two different lipid emulsions on morbidities and oxidant stress statuses in preterm infants: an observational study. J Matern Fetal Neonatal Med 2018;31:850-6.
3. Ozkan H, Koksal N, Dorum BA, et al. New-generation fish oil and olive oil lipid for prevention of oxidative damage in preterm infants: Single center clinical trial at university hospital in Turkey. Pediatr Int 2019;61:388-92.
4. Ernst KD. Essential fatty acid deficiency during parenteral soybean oil lipid minimization. J Perinatol 2017;37:695-7.
5. Deshpande G, Simmer K, Deshmukh M, et al. Fish Oil (SMOFlipid) and olive oil lipid (Clinoleic) in very preterm neonates. J Pediatr Gastroenterol Nutr 2014;58:177-82.
6. Molina TL, Stoll B, Mohammad M, et al. New generation lipid emulsions increase brain DHA and improve body composition, but not short-term neurodevelopment in parenterally-fed preterm piglets. Brain Behav Immun 2020;85:46-56.
7. Uauy R, Hoffman DR, Peirano P, et al. Essential fatty acids in visual and brain development. Lipids 2001;36:885-95.
8. Yaqoob P. Fatty acids and the immune system: from basic science to clinical applications. Proc Nutr Soc 2004;63:89-104.
9. Lavoie PM, Lavoie JC, Watson C, et al. Inflammatory response in preterm infants is induced early in life by oxygen and modulated by total parenteral nutrition. Pediatr Res 2010;68:248-51.
10. Adolph M. Lipid emulsions in parenteral nutrition—state of the art and future perspectives. Clin Nutr 2001;20:14-24.
11. Krohn K, Koletzko B. Parenteral lipid emulsions in paediatrics. Curr Opin Clin Nutr Metab Care 2006;9:319-23.
12. Waitzberg DL, Torrinhas RS, Jacintho TM. New parenteral lipid emulsion for clinical use. J Parenter Enteral Nutr 2006;30:351-67.
13. Koletzko B. Parenteral lipid infusion in infancy: physiology basis and clinical relevance. Clin Nutr 2002;21:53-6.
14. Gallacher DJ, Hart K, Kotecha S. Common respiratory conditions of the newborn. Breathe (Sheff) 2016;12:30-42
15. Principi N, Di Pietro GM, Esposito S. Bronchopulmonary dysplasia: clinical aspects and preventive and therapeutic strategies. J Transl Med 2018;16:36
16. Evans N. Diagnosis of the preterm patent ductus arteriosus: clinical signs, biomarkers, or ultrasound? Semin Perinatol 2012;36:114-22.
17. Papile LA, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-34
18. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1-7.

19. Fierson WM, American Academy of Pediatrics Section on Ophthalmology; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2013;131:189-95.
20. Feldman AG, Sokol RJ. Neonatal Cholestasis. Neoreviews 2013;14:10.
21. Beken S, Dilli D, Fettah ND, et al. The influence of fish-oil lipid emulsions on retinopathy of prematurity in very low birth weight infants: a randomized controlled trial. Early Hum Dev 2014;90:27-31.
22. Park HW, Lee NM, Kim JH, et al. Parenteral fish oil-containing lipid emulsions may reverse parenteral nutrition-associated cholestasis in neonates: a systematic review and meta-analysis. J Nutr 2015;145:277-83.
23. Skouroliakou M, Konstantinou D, Agakidis C, et al. Cholestasis, bronchopulmonary dysplasia, and lipid profile in preterm infants receiving MCT/ω-3-PUFA-containing or soybean-based lipid emulsions. Nutr Clin Pract 2012;27:817-24.
24. Panfoli I, Candiano G, Malova M, et al. Oxidative Stress as a Primary Risk Factor for Brain Damage in Preterm Newborns. Front Pediatr 2018;6:369.
25. Drenckpohl D, McConnell C, Gaffney S, et al. Randomized trial of very low birth weight infants receiving higher rates of infusion of intravenous fat emulsions during the first week of life. Pediatrics 2008;122:743-51.
26. Koletzko B, Goulet O, Hunt J, et al. Parenteral Nutrition Guidelines Working Group; European Society for Clinical Nutrition and Metabolism; European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN); European Society of Paediatric Research (ESPR). 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr 2005;41:1-87.
27. Correani A, Giretti I, Antognoli L, et al. Hypertriglyceridemia and Intravenous Lipid Titration During Routine Parenteral Nutrition in Small Preterm Infants. J Pediatr Gastroenterol Nutr 2019;69:619-25.
28. Sinclair R, Schindler T, Lui K, et al. Hypertriglyceridaemia in extremely preterm infants receiving parenteral lipid emulsions. BMC Pediatr 2018;18:348.
29. Holtrop P, Swails T, Riggs T. Hypertriglyceridemia in extremely low birth weight infants receiving lipid emulsions. J Neonatal Perinatal Med 2015;8:133-6.
30. Teng J, Arnell H, Bohlin K, et al. Impact of parenteral fat composition on cholestasis in preterm infants. J Pediatr Gastroenterol Nutr 2015;60:702-7.
31. Colomb V, Jobert-Giraud A, Lacaille F, et al. Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children. J Parenter Enteral Nutr 2000;24:345-50.
32. Rollins MD, Ward RM, Jackson WD, et al. Effect of decreased parenteral soybean lipid emulsion on hepatic function in infants at risk for parenteral nutrition-associated liver disease: a pilot study. J Pediatr Surg 2013;48:1348-56.
33. Lam HS, Tam YH, Poon TCW, et al. A double-blind randomised controlled trial of fish oil-based versus soy-based lipid preparations in the treatment of infants with parenteral nutrition-associated cholestasis. Neonatology 2014;105:290-6.