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YENİDOĞAN YOĞUN BAKIM ÜNİTESİNDE KULLANILAN FARKLI TİP LİPİD SOLÜSYONLARININ PREMATÜR BEBEKLERDE MORBİDİTELERİ VE OKSİDAN-ANTİOKSİDAN SİSTEMİ ÜZERİNE ETKİNLİĞİNİN ARAŞTIRILMASI

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Öz

Total parenteral beslenmede kullanılan SmofLipid ve İntraLipid solüsyon tiplerinin prematür doğan bebeklerde kullanımının morbiditeler ile birlikte oksidan ve antioksidan sistemi üzerine etkilerini araştırmaktır. Bu randomize kontrollü tek kör prospektif bir çalışma Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesinde yapıldı. Bebekler SMOFlipid (n=33) veya İntralipid (n=32) aldı. Başlangıçta ve lipid infüzyonunun 7. gününde alınan örnekler ile laboratuvar tetkikleri ve toplam antioksidan kapasitesi (TAK) ve toplam oksidan kapasite (TOK) ve oksidatif stres indeksi (OSI; TAK/TOS/100) çalışıldı. Her iki gruba da en az 7 gün boyunca parenteral beslenme desteği verildi. Üzerinde inceleme yapılan demografik özelliklerin birçoğunda gözlenen değerler ile beklenen değerler arasında istatistiksel olarak önemli bir fark bulunmazken ($p>0.05$) CPAP süresi ve yatış süresinin gözlenen değerler ile beklenen değerler arasında istatistikî olarak önemli bir fark bulunmuştur ($p<0.05$). Her iki grup arasında morbiditeler açısından gözlenen değerler ile beklenen değerler arasında istatistikî açıdan önemli bir farklılık bulunmamıştır. 1 hafta sonra her iki grupta da grubunda TAK değerinde artma, TOK ve OSI değerlerinde azalma olduğu gözlemlendi ve sonuçlar istatistiksel olarak anlamlı fark bulunmamıştır. ($p>0.05$). SMOFlipid ve İntraLipid solüsyonları verildikten sonra benzer oksidatif stres durumları olduğu tespit edilmiştir ve morbidite oranlarında istatistiksel olarak anlamlı bir farklılık tespit edilmemiştir**.**

Anahtar Kelimeler: Total parenteral beslenme, lipid solüsyonu, prematür, oksidatif stres

INVESTIGATION OF THE EFFECTS OF DIFFERENT LIPID SOLUTIONS USED IN NEONATAL INTENSIVE CARE UNIT ON MORBIDITIES AND OXIDANT-ANTIOXIDANT SYSTEMS OF PREMATURE BABIES

Abstract

To investigate the effects of using SmofLipid and IntraLipid solutions in total parenteral nutrition of premature babies on their morbidities and oxidant-antioxidant systems. This randomized, controlled, single-blind prospective study was conducted in Zekai Tahir Burak Gynaecology Training and Research Hospital. The babies received either SMOFlipid (n=33) or Intralipid (n=32). With the samples taken at baseline and at day 7 of lipid infusion, the laboratory tests and the total antioxidant capacity (TAC), total oxidant capacity (TOC) and oxidative stress index (OSI: TAC/TOC/100) were studied. Parenteral nutrition support was provided to both groups for at least 7 days. While no statistically significant differences were found between the observed values and expected values in most of the demographic characteristics studied ($p>0.05$), a statistically significant difference was found between the observed values and expected values of the length of CPAP and length of hospitalization ($p<0.05$). No statistically significant difference was found between the observed values and expected values with respect to morbidities between the two groups. A week later, an increase in the TAC values and a decrease in the TOC and OSI values were observed in both groups, and the results were found no statistically difference between them ($p>0.05$). Similar oxidative stress conditions were found after giving SMOFlipid and IntraLipid solutions and no statistically significant difference was found in morbidity rates.

Keywords: Parenteral nutrition, Total, lipid emultion, premature birth, oxidative stress

1. INTRODUCTION

Due to their immature antioxidant systems, premature babies are vulnerable to common morbidities associated with oxidative damage and inflammation such as bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC), persistent ductus anteriosus (PDA), and premature retinopathy (ROP) (1.2). With an increase in this probability of oxidative damage, formation of reactive oxygen species also increases and the condition may worsen with medical interventions such as positive pressure ventilation (3-5).

Many antioxidant strategies used so far could not successfully reduce oxidative stress and resulting neonatal diseases associated with free radicals and could not meet the need for relief from other risk factors (6). In fact, premature babies are exposed to many oxidative stress-increasing risk factors such as phototherapy, formula feeding and oxygen therapy (7,8).

Total parenteral nutrition (TPN) we often use in premature babies is another risk factor increasing oxidative stress (9). The lipid solutions used for parenteral nutrition in neonatal intensive care units (NICU) can be administered by mixing them in a TPN bag or separately. These standard lipid solutions contain a soy bean oil or an olive oil mixture (IntraLipid®- 20% soy-based or Clinoleic®- 20% olive oil-based), both of which can affect oxidative stress (10,11). SMOFlipid® 20% solution, on the other hand, contains soy bean oil, medium-chain fatty acids, olive oil and fish oil. It varies from other lipid solutions due to its rich omega-3 fatty acid plus α-tocopherol content (12). It has been shown that SMOFlipid solution can reduce the incidence of lipid peroxidation and oxidative stress-associated morbidity (11).

Oxidant-antioxidant balance is important in premature babies. For this reason, this study aimed at comparing the effects of SMOFLipid and IntraLipid solutions that are used for TPN in babies with very low birth weight (VLBW) on the total oxidant capacity (TOC) and total antioxidant capacity (TAC) levels and exploring their relationship with morbidities that are thought to be associated with oxidative damage.

2. MATERIALS AND METHODS

Our study was conducted as a randomized controlled single-blind prospective study. Randomization was carried out using the blockage (according to birth weight and gender) and closed envelope method. Before enrolment, a written informed consent was obtained from the parents after providing them with detailed information about the goals and risks involved in the study and reminding them that they had the right to withdraw their children from the study any time they wished. Approval from the Local Ethics Committee of our hospital was obtained for the study.

The study included premature patients at ≤32 weeks of gestation and/or weighing ≤1500 gm who were born and bedded in the neonatal clinic of Zekai Tahir Burak Gynaecology Training and Research Hospital between January 2014 and July 2014. During the preliminary works (day 0), the patients' demographic data, medical histories, accompanying diseases and medications of the babies were recorded. Clinical assessments were performed daily starting from day 0. Babies with asphyxia, intrauterine development retardation, a major surgical disease of the gastrointestinal system, critical congenital heart disease, a major congenital abnormality, and congenital metabolic disease were excluded from the study.

A 1 gm/kg dose of TPN containing an amino acid solution (Primene® 10%, Clintec Parenteral, Maurepas, France) was started at day 1 of hospitalization. The protein content of TPN was gradually increased up to 4 gm/kg. The ingredients of the two different types of lipid solutions used are given in Table 1.

Table 1. Lipid Emulsions Used in the Study and Their Oil Contents

Product name	Soy Bean Oil (LCT)	Coconut oil (MCT)	Olive oil	Fish oil
Intralipid ®	100	0	0	0
SmofLipid ®	30	30	25	15

LCT: Long-chain fatty acids, MCT: Medium-chain fatty acids

Babies who competed their first 24 hours were started a 1 gm/kg dose of lipid solution, which was increased to a maximum of 3 gm/kg/day in daily increments of 1 gm/kg. The lipid solutions were delivered in 24-hour infusions. Lipid solutions were continued until day 7 or day 14 of life. Enteral nutrition with 10 cc/kg/day of mother's milk was started from day 2 of life and gradually increased to 20 cc/kg/day. While increasing enteral feeding, a proportional amount of TPN was decreased gradually.

The TPN solutions were prepared using an automatic filling system in our TPN unit (Exacta-Mix™ compounder system, Baxa Corporation, USA) in a clean room. As per the protocol used in our unit, lipid solutions are prepared by an automatic filling system with light-protected injectors without exposing to air or adding any trace elements. The SMOFLipid® (study group n=32, %20; Fresenius Kabi, Bad Homburg, Germany) and IntraLipid® (control group n=33, %20; Fresenius Kabi, Bad Homburg, Germany) lipid solutions were used in the study. Each lipid solution type was coded using a closed envelope method and was prepared and labelled by a single independent member of the pharmacy staff.

Two ml of blood samples were taken at baseline and day 7 of lipid solution infusions and were centrifuged at 3600 cycles for 10 minutes for safety and efficacy assessments. The supernatants were kept in Eppendorf tubes at -80 degrees until measurements. The plasma TAC (mmol Trolox equivelent/L), TOC (µmol H2O2/L) and Oxidative Stress Index (OSI) values were studied with Rel Assay Diagnostics kits using the automatic colorimetric measurement method developed by Erel in Turkey (13,14). In calculating OSI, which is an indicator of the degree of total oxidative stress, the TOC/TAC/100 formula was used (OSI = (TOK, µmol/L)/(TAK, µmol Trolox equivalent/L/100)). At day 7, a few drops of blood samples were put on a piece of Guthrie paper and acyl carnitine levels were sent for plasma lipid levels and tandom mass spectrophotometry (API 3200, Shimadzu, Applied Biosystems, USA).

The primary endpoint in this study was to evaluate the oxidative stress in premature infants by measuring concentrations of TAC, TOC and OSI levels and the secondary endpoints were to assess the other laboratory data (Hemogram data, C-Reactive Protein (CRP), Interleukin-6 (IL-6), Triglyceride (TG), and free carnitine levels), duration of ventilation days and oxygen therapy, presence of significant haemodynamic PDA being treated, presence of intracranial bleeding (ICB), late-onset neonatal sepsis (clinical or evidenced between days 4 and 120 of life), NEC (Stage 2), presence of cholestasis, hospital stay, BPD (oxygen dependency after week 36 of postmenstrual age), ROP (requiring laser therapy) and mortality.

IBM SPSS version 23.0 (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses. Chi-square and Fisher Exact tests were used for comparisons of categorical propositions. The Shapiro Wilk values in the normality test results showed that the continuous measurements did not have a normal distribution and the Mann Whitney-U test was used to analyse the related parameters. Categorical variables were presented as numbers (N) and percentages (%). Wilxocon test was used for the measurements before and after laboratory results. Statistical significance was set at $p<0.05$ in all tests.

3. RESULTS

Throughout the study, 101 premature babies with VLBW were enrolled for the study. Of these babies 65 were included in the study (SMOFLipid: n=32 and and IntraLipid: n=33). A total of 36 babies who had perinatal asphyxia (n=4), a major congenital anomaly (n=8), a congenital heart disease (n=6), intrauterine development retardation (n=16), and those who were infused with both lipid solutions (n=2) were excluded from the study. No statistically significant difference was found between the two groups with respect to their antenatal and clinical characteristics (Table 2).

Table 2. Antenatal and Clinical Characteristics of Patients

Variables	SMOFLipid (n=32)	İntraLipid (n=33)	p
Mother's age (age)	30 (16-41)	30 (23-41)	0.906
Gestational week (week)	28 (25-32)	28 (24-32)	0.417
Birth weight (gm)	1050 (595-2200)	1100 (480-1480)	0.665
Male gender, %	18/32 (56)	17/33 (51)	0.811
Caesarean section, %	25/32 (78)	24/33 (72)	0.527
APGAR 1. minute	5 (1-7)	6 (1-7)	0.524
APGAR 5. minute	7 (1-9)	8 (3-9)	0.428
Multiple pregnancy	7/32 (21.9)	12/33 (36.4)	0.277
Antenatal steroid	9/32 (28.1)	10/33 (30.3)	NA
PPROM	4/32 (12.5)	6/33 (18.2)	0.733
Oligohydramnios	2/32 (6.3)	5/33 (15.2)	0.427
Pregnancy hypertension	1 (3.1)	0 (0)	0.492
Preeclampsia in mother	4 (12.5)	3 (9.1)	0.708
Diabetes in mother	2 (6.3)	1 (3.0)	0.613
Hyperthyroidism in mother	1 (3.1)	3 (9.1)	0.613
RDS	29/32 (90)	28/33 (84.8)	0.810
Surfactant	15/32 (46.9)	21/33 (63.6)	0.148
Early sepsis	5/32 (15.6)	4/33 (12.1)	0.437
Pneumothorax	0/32 (0)	2/33 (6.1)	0.492
Length of TPN, days	8 (7-11)	8 (6-12)	0.098

TPN: Total parenteral nutrition, RDS: Respiratory distress syndrome, PPROM: Preterm premature rupture of membrane

The length of TPN was similar in both groups [SMOFLipid: 8 (7-11) days and IntraLipid 8 (6-12) days; p = 0,098]. No statistically significant difference was found between the two groups with respect to mortality and other clinical results including BPD, ROP and late-onset sepsis (Table 3).

Table 3. Clinical Outcomes of Patients

Variables	SMOFLipid (n=32)	İntraLipid (n=33)	p
Late neonatal sepsis	7 (21.9)	12 (36.4)	0.437
Patent Ductus Arteriosus	11 (34.4)	14 (42.4)	0.612
Intracranial Bleeding			
None	9 (28.1)	7 (21.2)	
Grade 1-2	19 (59.4)	25 (75.8)	0.240
Grade 3-4	4 (12.5)	1 (3)	
Premature Retinopathy	10 (31.3)	12 (36.4)	0.794
Premature Retinopathy			
No	22 (68.8)	21 (63.6)	
Yes	9 (28.1)	9 (27.3)	0.604
Laser	1 (3.1)	3 (9.1)	
Necrotizing Enterocolitis Stage 2 and above	6 (18.8)	4 (12.1)	0.511
Bronchopulmonary dysplasia	4 (12.5)	4 (12.1)	NA
No cholestasis	32 (100)	33 (100)	NA
Premature osteopenia	3/32 (9.4)	2/33 (6.1)	0.672
Length of mechanical ventilation	19 (0-38)	17 (0-34)	0.807

Length of nasal CPAP	3 (0-64)	5 (0-52)	0,456
Length of oxygen	1.5 (0-45)	5 (0-86)	0.158
Hospital stay	37 (1-129)	59 (4-161)	0.223
Mortality	9 (28.1)	5 (15.2)	0.240

Whether there was a statistical difference between the TAC, TOC and OSI levels, and the other laboratory values (including TG) measured at baseline and at day 7 of lipid solution (before and after) was evaluated (Table 4).

Table 4. Laboratory Values Before And After Lipid Emulations

Variables	SMOFLipid (n=32)	İntraLipid (n=33)	p
WBC_1	12.35 (6.1-71)	8.53 (4-23.3)	0.432
WBC_2	14.7 (6-65.8)	13 (6.63-49)	0.443
HB_1	16.55 (13-23)	17 (12.8-22.5)	0.516
HB_2	14.5 (9-19.2)	14 (7.1-18.4)	0.176
PLT_1	235.500 (96.000-371.000)	234.000 (140.000-442.000)	0.854
PLT_2	183 (74-559)	251 (104-625)	0.058
CRP_1	1.20 (0.23-9.12)	0.61 (0.27-13.6)	0.096
CRP_2	3.28 (0.74-112)	1.83 (0.13-01.29)	0.102
IL-6_1	38.9 (4.66-5000)	61.22 (2.77-5000)	0.586
IL-6_2	20.16 (4-250)	15 (1.5-200)	0.932
TG_1	38 (26-171)	36 (16-185)	0.245
TG_2	86 (35-1726)	89 (29-735)	0.906
TAC _1	2.03 (1.36-3.35)	2.01 (1.09-2.71)	0.703
TAC _2	2.26 (1.36-3.24)	2.21 (2-2.99)	0.768
TOC_1	4.71 (0.58-11.01)	2.82 (0.55-11.48)	0.187
TOC_2	1.98 (0.14-10.29)	2 (0.19-9.89)	0.180
OSI_1	0.22 (0.020-0.66)	0.16 (0.03-0.51)	0.434
OSI_2	0.08 (0.01-0.49)	0.09 (0.01-0.37)	0.138
Free carnitine_1			
Normal	29 (90.6)	32 (97)	0.287
High	3 (9.4)	1 (3)	
Free carnitine_2			
Low	5 (16.7)	1 (3.3)	0.195
Normal	25 (83.3)	29 (96.7)	

WBC: White blood cell, HB: Hemoglobin, PLT: Platelet count, CRP: C-reactive protein, IL-6: Interleukin-6, TG: Triglyceride, TAC: Total antioxidant capacity, TOC: Total oxidant capacity, OSI: Oxidative stress index.

No similarity was found in baseline TAC, TOC and OSI values (p >0,05). A comparison of the values at week 1 after the baseline between the two groups showed a decrease in TAC values and an increase in TOC and OSI values, but the difference was not statistically significant (p>0.05). No statistically significant difference was observed between the free carnitine levels measured at baseline and at week 1 (p>0.05).

4. DISCUSSION

Oxidative stress is a physiological event taking place during fetal-neonatal transition. This process is held responsible for many pathological conditions seen in newborns. The most important one of these is the immature antioxidant system of premature babies. Exposure to hyperoxia is also thought to induce oxidative stress. Due to increased oxidative stress, premature babies are prone to many serious morbidities associated with oxidative damage and inflammation including RDS, BPD, ICB and ROP.

Lipid solutions are given to deliver many important essential fatty acids needed for the development of premature babies, their immune response, and produce significant phagocytic function and bioactive substances (15). There are various lipid solutions with varying ingredients. Soy bean oil solution (IntraLipid®) contains plenty of bioactive and essential polyunsaturated fatty acids with small content of α-tocopherol. But olive oil-based solutions (ClinOleic®) include higher proportion of α-tocopherol and monounsaturated fatty acids with smaller amounts of polyunsaturated fatty acids. SMOFLipid, a new solution, has the highest amounts of omega-3 and α-tocopherol between the two products; and most importantly, these components are not only known for their antioxidant effects but are also shown in studies to be safe and effective in premature babies (16). Still, there is no strong data showing the possible health benefits of using SMOFLipid in premature babies (16-19).

This study explored the relationship between the lipid solutions given and the recovery in the antioxidant system. Assuming that antioxidant defence mechanisms become stronger in the group receiving omega-3 lipid solution, the pre-treatment and post-treatment TAC, TOC and OSI levels were compared between the group taking SMOFLipid®, which contains fish oil, and the group taking IntraLipid®, which contains soy bean oil, but no statistically significant difference was found ($p>0.05$).

This study is one of the few studies comparing the results of oxidative stress statuses and free radical-associated morbidity rates by using IntraLipid and SMOFLipid solutions among VLBW premature babies. This study also investigated oxidative stress-related morbidities, which are already known conditions such as sepsis, stage 3 ICB, ROP, BPD, PDA, NEC and cholestasis or which may come up as a potential condition. In the presence of so many oxidative stress conditions in premature babies receiving SMOFlipid and IntraLipid solutions, risks of secondary morbidities that may occur were listed. No significant differences were found between the morbidities in the two groups.

TG levels should be carefully monitored during and after lipid solution infusions. Due to their limited muscle and fat masses and resulting decrease in the hydrolytic capacity of lipoprotein lipase enzyme, premature babies are at higher risk of hypertriglyceridemia than full term babies (20,21). SMOFLipid has been shown to be eliminated considerably faster than a standard lipid solution in healthy individuals, proving that it provides a potential benefit in patients with limited TG elimination capacity (22). For paediatric PN, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition recommends a reduction of the lipid solution dose if serum TG concentration exceeds 250 mg/dL (20). In the present study, both lipid solutions were found safe in this respect and although the intravenous lipid infusion were given up to 3 gm/kg per day, premature babies were observed to tolerate them well.

While fish-oil based lipid solutions were shown to have benefits for reversing TPN-associated cholestasis in some studies (23), some other studies concluded that they may have a preventive effect (24,25). No cholestasis occurred in any of the groups in our study.

One of the limitations of the study is that the sample studied was small. It was extremely difficult to include more subjects in the study due to the characteristics of the study group and strict

exclusion criteria. Another limitation is that a few of the biomarkers of oxidative stress were evaluated, which can restrict the interpretation of the results. However, the amount of blood taken for our study was limited due to the ages of the subjects studied.

This study reveals that using SMOFLipid solution did not have any positive effect in morbidities. According to this research protocol, the patients had shorter TPN periods contrast to other similar research studies, which prevents direct comparisons; by reducing TPN exposure and thereafter declining the development of oxidizing events, shorter periods may limit oxidative stress. To evaluate actual effects of SMOFLipid solution on health consequences, there is a need for further randomized controlled studies involving a larger sample of premature babies receiving TPN for longer periods.

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