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Parenteral lipid nutrition in congenital gastrointestinal malformation operated cases

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Abstract

Background: Congenital gastrointestinal malformation (CGIM) cases require immediate surgical correction after birth and proper nutrition to meet energy demands. Among the macronutrients, lipids are considered the major energy source, playing a vital role in parenteral nutrition. However, the time of their initiation remains unclear. We compared the data of CGIM cases where lipids were given from the first post-surgical day to those where parenteral lipids were initiated on the second or third day of surgery and then reevaluated them on the seventh day of parenteral nutrition.

Methods: We collected the data of patients who had undergone surgical correction for CGIM and were kept on parenteral nutrition including lipids from day 1 of surgery labeling them as group 1. Group 2 comprised of neonates having lipid parenteral nutrition started from day 2 or 3 of surgery. Both groups were reevaluated on the 7th day of parenteral nutrition. Statistical analysis was performed.

Results: Group 1 had higher total bilirubin (TB) statistically significant (p-value=0.0299), as well as lower lipase (p-value=0.0286), and lower total lipids (p-value=0.0365). The values were lower of triglycerides (p-value=0.0365), and total lipids (p-value=0.0365), on day 1. Comparing both groups, all biochemical parameters were found to be statistically significant.

Conclusion: Lipid deficiency and overload should be carefully evaluated, especially in neonates having undergone recent surgical interventions, which increase their nutritional demands. No adverse effects were seen in our study related to parenteral lipid emulsion administration in post-surgical congenital gastrointestinal malformation cases. Early initiation of parenteral lipid regimens can provide better outcomes.

Introduction

Congenital malformations (CM) are defined as morphological defects of an organ or the system resulting from intrinsic abnormal developmental issues during intrauterine life. The World Health Organization (WHO) estimates state that annually, worldwide, almost 240,000 newborns die from congenital malformations before reaching the age of 28 days, and around 170,000 children die from similar causes between the ages of 1 month to 5 years. Although, cardiac congenital malformations and neural tube defects are at the top of the list of congenital malformations and are considered to have high mortality rates [1,2].

Congenital gastrointestinal malformations (CGIM) can affect the esophagus, stomach, small intestine, large intestine, or the anus. Most often, these defects occur during the development of the embryo causing improper positioning, poor development, and growth interruptions of the organs resulting in abnormal formation of the digestive system [3]. These damages hinder the proper functioning of the digestive tract, leading to high mortality and morbidity in neonates and exhibiting a wide variety of complications. Some long-term complications affect the quality of life (QOL) of the child and of the relatives throughout life. Financial burden on the healthcare system is also a major concern in CGIM cases [4].

A wide variety of CGIM can be witnessed ranging from developmental defects like agenesis, aplasia, or atresia. They are alternatively, resulting from an excess of the developmental processes as seen in cases of segmental duplications of the digestive tube. The processes of malrotation may or may not be associated with coalescence defects, and as a result, various problems might appear such as anomalies located to the positioning of the organs or structures. Among the congenital anomalies having histological and genetically driven defects as their etiology include: Hirschsprung's disease and cystic fibrosis [5].

Prenatal ultrasound (PN-US) is considered to be one of the most efficient tools in detecting a vast range of CGIM. The suspected diagnosis of any such abnormality should be verified with caution, as chances of having false positive or false negative results are quite high, hence an expert having the dexterity in this field can help minimize the misdiagnosis. For example, the pathological processes located at the level of the other organs can appear during ultrasound examinations similar to the image of a dilated intestine and should be properly ruled out [6]. Once the diagnosis is established, immediate surgical correction remains the only weapon after birth, to increase the survival chances in the majority of the cases of CGIM [7]. Initiation of enteral nutrition within the first 48-72 hours in the postoperative period in CGIM babies is recommended to avoid the need for long-term total parenteral nutrition and to minimize possible complications [8]. Breastfeeding remains the first choice; if it is not an option then a standard milk formula should be considered. Sometimes for proper replenishment of the energy stores, early initiation of the parenteral nutrition becomes mandatory, until the final goal of complete enteral nutrition is achieved. Nutritional complications often occur in this vulnerable category of newborns. The overall weight and height growth curve is highly influenced in CGIM operated children and lack of proper care can further lead to long-term effects [9]. Associated malformations worsen further the negative impact on the growth of the operated newborns. Genetic syndromes found in some patients comprise the respiratory, gastrointestinal complications necessitating repeated surgical interventions due to adhesions.

To ensure proper growth and development and energy requirements of the growing newborn macronutrients (proteins, carbohydrates, and lipids) play a pivotal role [10,11]. Since optimal nutritional management becomes crucial in neonates with CGIM to support growth and development, and to fight the surgical stress as majority of the pathologies necessitate surgical procedures, to promote healing, and to prevent complications. Nutritional strategies often involve a combination of enteral and parenteral nutrition, tailored to the specific malformation and individual needs of the infant [12]. Accurate assessment of macronutrient requirements, precise formulation of enteral and parenteral feeds, and careful monitoring of nutritional status are all vital components of the management plan [12-14]. Lipids are vital for proper growth, further; they are a source of fatty acids, fat-soluble vitamins, and structural and functional components of membranes, having a role directly in gene regulation [15,16]. Lipid administration is of prime importance due to its high caloric content which helps in preventing essential fatty acid (EFA) deficiency and acts as a vehicle for fat-soluble vitamins. Lipid emulsions play an important role in the parenteral nutrition (PN) of newborns. Similarly, studies have demonstrated that using fats in parenteral nutrition helps reduce overall energy consumption [17,18]. However, conventional use of soybean oil-based lipid emulsions (S-LE), containing large amounts of phytosterols and polyunsaturated fatty acid (PUFA) might contribute to negative effects in neonates and are capable of causing PN-associated liver disease (PNALD) [19]. There are studies suggesting that lipid infusions if not properly monitored can worsen lung disease, bilirubin displacement from albumin, thrombocytopenia, or sepsis. Other adverse effects of

intravenous lipid emulsions, such as hyperglycemia, hypertriglyceridemia, and hyperlipidemia have been observed, depending on the type of lipid emulsion used on neonatology units [20].

Dyslipidemia can be defined as higher-than-normal values of low-density lipoprotein – cholesterol (LDL - C) and triglycerides (TG) (>90th percentile for age and gender) and/or low levels of high-density lipoprotein – cholesterol (HDL - C) [21]. The average total cholesterol value in a newborn is 70 mg/dL (1.8 mmol/ L), and LDL cholesterol is reported as 23,8 ± 10,62 mg/dL (0.62 ± 0.27 mmol/L) in males and 25,5±9,29 mg/dL (0.65 ± 0.24 mmol/L) in female neonates [22]. According to international reference values, the mean cord blood level of TC is 68mg/dL, which is doubled during the neonatal period. Mean cord blood levels of other parameters like TG, HDL – C, and LDL - C are 34mg/dL, 35mg/dL, and 29mg/dL respectively. The safe level of LDL-C typically in newborns ranges from 20–40 mg/dL above which level, atherosclerosis becomes more common [23]. In a study conducted by Sandstorm K. et al. the blood concentration of TG, FFA, and 3-hydroxybutyrate was significantly higher in post-surgical neonatal cases receiving lipid emulsions, while at the same time, there was no accumulation of linoleic and palmitic acid noted [24]. However, there are not many studies focusing on the time of initiation of the lipids post-surgically.

Post-gastrointestinal surgery complications can include the formation of ileus due to a delay in bowel motility. Choosing the correct type and proper dose of fluids can reduce the chances of developing ileus in the postoperative period. Although still there are many controversies regarding this [25]. Studies state that it is better not to provoke excessive fluid intake, and it is recommended to be 160–170 mL/kg/day. Hence, fluid administered by PN should be carefully monitored to avoid fluid overload but also at the same time, it should be sufficient enough to avoid macronutrient deficiency [26,27].

Complications due to lipid parenteral nutrition in the neonatal period: various complications can be witnessed due to the excessive use of PN. On one hand, parenteral lipids are considered to be vital sources of calories, they help in improving metabolic efficiencies, and additionally prevent essential fatty acid deficiencies. They have the potential to cause an increase in the triglyceride levels and or cause an increase in blood glucose levels [28]. Commonly mild increase in blood glucose is seen (>150 mg/dl (8.3 mmol/L)) [29] or sometimes even it can decrease glucose levels (BGL < 2.6mmol/L) [30]. Hence, ESPGHAN 2005 Guidelines have recommended keeping a close check of triglycerides in preterm babies and term infants and have also indicated a triglyceride level of 2.8mmol/L as the upper limit and termed hypertriglyceridemia (HT) when their levels are more than 2.8 mmol/L of the triglycerides [31]. A study demonstrated that HT can be associated with a significant increase in mortality and severe retinopathy of prematurity on univariate analysis [32]. Additionally, excess carbohydrate intake can lead to excessive lipogenesis and contribute to hypertriglyceridemia. The definition of cholestasis includes having direct serum bilirubin > 20% of total serum bilirubin or direct serum bilirubin > 34 mcmol/L [mg/dL x 17.10] [33]. Liver injury due to intravenous lipids is supposed to be due to the hepatocytes receiving lipids at a rate faster than their ability to clear. This results in the accumulation of phospholipids and fatty acids from the lipid molecules into the hepatocytes and Kupffer cells [34]. A study states that intravenous lipid emulsions are well tolerated by neonates and the carbon dioxide lowering effects are due to carbohydrate conversion to fat, especially in neonates having respiration comorbidities [35]. Studies also state that administering long-chain triglycerides as a partial substitute by medium chain can further enhance fat oxidation better in post-surgical neonatal cases [36].

The main goal of our study was to monitor the changes seen in biochemical parameters of severe neonatal cases who are kept on parenteral nutrition including lipid emulsions. As well as to observe adverse effects of early initiation of parenteral lipid emulsion in post-operative patients.

Methods

We collected the data of newborns having congenital gastrointestinal malformation who were admitted from January 2023 to March 2024 in our "Louis Turcanu" Children's Emergency Clinical Hospital Timisoara. We collected data of patients who had undergone surgical correction for CGIM and were kept on parenteral nutrition including lipids from day 1 of surgery, labeling them as group 1a. And neonates that received lipid infusions on day 2 or 3 of surgery labeling them as Group 2a. Further we reevaluated both the groups on the 7th day of parenteral nutrition and labelled them as group 1b, and group 2b. Neonates were administered with parenteral lipid formulation "SMOFlipid" which is a mixture of soybean oil, medium chain triglycerides (MCT), and olive oil (OO). The initial dose administered was 1g/kg/day initially, with a daily increase of 0.5 g/kg/day until the maximum dose of 3g/kg/day. Usually, the lipids were administered preferably for 7 days, keeping in mind the complication neonate might suffer if given for a prolonged duration of time, especially when exceeding 14 days. The duration of lipid administration was purely case-dependent.

Laboratory investigations to see any changes in liver enzymes like ALT, AST, GGT, alkaline phosphatase, lipid profile, etc. were performed daily to rule out any side effects of intravenous parenteral nutrition like cholestasis. We performed a statistical analysis comparing individually and together the parameters of both the groups to see the outcomes of growth and development and hospital stay and for possible side effects.

The study was conducted with the approval of the Ethics Committee for Scientific Research of the "Louis Turcanu" Children's Emergency Clinical Hospital Timisoara (PRM/453/6.07.2023 reg. no. 10594/06.07.2023). Additionally, written informed consent for the conduct of the study was obtained from the parents/legal guardians of the children included in the study.

Inclusion Criteria and Study Variables

The study included all newborns who underwent surgical intervention in our hospital in the Pediatric Surgery Department and were transferred within the first 24 hours after the intervention to the Neonatal Intensive Care Department and further received parenteral lipid nutrition starting from day 1, 2, or 3 post-surgically.

Exclusion Criteria

Newborns with digestive malformations suffered mortality during or before the surgery. Neonates having sepsis, and severe congenital cardiac or neurological malformations were also excluded from the study. Newborns discharged 7 days of hospitalization or those not receiving parenteral nutrition also were excluded.

Blood Samples Collection

Blood samples were obtained between 6 AM and 8 AM, before the first morning feed. The samples were allowed to clot and then after centrifuging, the supernatant was collected. Total cholesterol, LDL-cholesterol, HDL-cholesterol, total and direct bilirubin, lipase, and triglyceride levels were measured on the day of initiation of lipid parenteral nutrition and after 7 days. Total cholesterol levels were determined by cholesterol oxidase/phenol + aminophenazone end-point enzymatic method. The detergent/dichromatic end-point method was used for high-density lipoprotein (HDL) cholesterol levels, while lipase/glycerol kinase dichromatic end-point method was used for determining triglyceride levels. The direct estimation method was used for LDL-cholesterol. All measurements were made using Cobas Integra 400 Plus in the authorized laboratory of the hospital.

The Measurements

Daily measurements were taken using the same digital scale every day at 10 am after feeds, and the results were recorded in the newborns' hospital observation chart.

Statistical Analysis

Test performed: Mann-Whitney test (independent samples) Compared values are based on medians. Chi-squared test for categorical values. The p-value of < 0.05 was considered significant.

Results

Based on the inclusion and exclusion criteria we collected data of 82 newborns having the diagnosis of CGIM and who had received post-surgical parenteral nutrition with lipids. The demographic data showed that 51.29% were male and were female 48.71%. 56.09% of neonates were born at term (GA$\geqslant$37 weeks) while 43.91% were premature babies. We had 58.53% cases from rural areas and the remaining 41.47% from an urban environment. The mode of birth was natural at 73.17% and the remaining 26.83% had been delivered by the cesarean section.

Comparisons of the general characteristics of the patients at the start of the study, weight at admission, gestational age, and biochemical data collected in the first 24 hours, before parenteral administration of lipids, duration of hospitalization, and complications of the groups during the hospitalization are presented in table 1. We can see that group 1 has higher total bilirubin (TB), statistically significant (p-value=0.0299), as well as lower lipase (p-value=0.0286), and lower total lipids (p-value=0.0365). Instead, it has lower values of triglycerides (p-value=0.0365), and total lipids (p-value=0.0365), as well as a longer duration of hospitalization (p-value=0.0496). We cannot notice a greater weight at admission between the two batches. In conclusion, there are no significant statistical differences between the two study groups. GA (IQR) was 37 weeks in both categories.

In addition, the levels of ALT and GGT were found in normal ranges and hence it can be stated that none of the patients from both groups suffered from cholestasis.

The type of digestive malformation witnessed varied. The most common malformation was esophageal atresia in 11%, followed by duodenal stenosis in 9.7% and ileal atresia in 8.5%. During hospitalization, frequent complications seen were respiratory distress syndrome in 30.5% of newborns, and maternal-fetal infection, confirmed by positive blood culture in 14.6%. In addition, inborn metabolic errors in 4.9% of cases were noted.

Parameters	Group 1a (n=41)	Group 2a (n=41)	p-value
GA (IQR) weeks	37 (34 to 38)	37 (34 to 38)	p-value= 1.0000
DB (IQR) mg/dl	0.42 (0.29 to 1.09)	0.75 (0.33 to 0.88)	p-value= 0.6033
TB (IQR) mg/dl	2.08 (0.55 to 3.85)	0.98 (0.83 to 1.20)	p-value= 0.0299
Total Cholesterol (IQR) mg/dl	78.8 (64.73 to 97.52)	90 (74.26 to 112.90)	p-value= 0.0147
LDL (IQR) mg/dl	1.01 (0.70 to 1.23)	0.92 (0.76 to 1.32)	p-value= 0.6394
HDL (IQR) mg/dl	1.01 (0.52 to 0.81)	0.92 (0.59 to 1.17)	p-value= 0.0398
Serum lipase (IQR) mg/dl	9 (7.00 to 11.00)	10 (9.00 to 13.00)	p-value= 0.0286
Total lipids (IQR) mg/dl	4.06 (3.37 to 4.52)	4.25 (3.82 to 4.68)	p-value= 0.0365
Triglycerides (IQR) mg/dl	1.01 (0.81 to 1.21)	1.25 (0.89 to 1.46)	p-value= 0.0365
Hospitalization days (IQR) days	23 (12.75 to 47.00)	20 (11.00 to 28.25)	p-value= 0.0496
Weight at admission (IQR) grams	2700 (2100 to 3000)	2690 (2165 to 3027)	p-value= 0.8930
Bronchopulmonary Dysplasia	3 /41 (7.3%)	7/41 17.1%	p-value= 0.1797
NEC (Necrotizing Enterocollitis)	2 /41 4.9%)	4/41 9.8%	p-value= 0.3993
ROP (Retinopathy of Prematurity)	4/41 9.8%)	7/41 17.1%	p-value= 0.3816
Sepsis	7 (17.1%)	7/41 17.1%	p-value= 1.0000
IVH (intraventricular hemorrhage)	7 (17.1%)	5/41 14.6%	p-value= 0.7156

Table 1: Comparison of blood parameters, presence of co-morbidities and general characteristics of both the groups included in the study are compared on the day of initiation of parenteral lipid nutrition. Test performed Mann-Whitney test (independent samples). Compared values are based on medians. Chi-squared was test for categorical values. The p-value of < 0.05 was considered significant. (GA: gestational age; DB: direct bilirubin; TB: total bilirubin).

Parameters	Group 1b (n=41)	Group 2b (n=41)	p-value
DB (IQR) mg/dl	0.31 (0.17 to 0.52)	0.34 (0.17 to 0.49)	p-value= 0.8637
TB (IQR) mg/dl	0.87 (0.32 to 1.98)	0.45 (0.30 to 0.60)	p-value= 0.0052
Total Cholesterol (IQR) mg/dl	96.50 (80.35 to 121.71)	102.50 (92.25 to 135.50)	p-value= 0.1259
LDL (IQR) mg/dl	1.13 (0.90 to 1.36)	1.25 (1.02 to 1.64)	p-value= 0.1075
HDL (IQR) mg/dl	0.82 (0.67 to 1.02)	0.95 (0.75 to 1.41)	p-value= 0.0347
Serum lipase (IQR) mg/dl	13 (12.00 to 14.00)	14 (12.00 to 16.00)	p-value= 0.1198
Total lipids (IQR) mg/dl	4.45 (4.20 to 5.23)	4.80 (4.40 to 5.65)	p-value= 0.0365
Weight at discharge (IQR) grams	3030.00 (2682.50 to 3372.50) 2	3100.00 (92787.50 to 3400.00)	p-value= 0.6063

Table 2: Comparisons of blood parameters on the 7th day of lipid administration and their weight on discharge, in both the groups. (DB= direct bilirubin; TB= total bilirubin; lipid profile) Test performed Mann-Whitney test (independent samples) Compared values are based on medians. The p-value of < 0.05 was considered significant. (DB= direct bilirubin; TB= total bilirubin; lipid profile).

Group 1	Group 1a (n=41)	Group 1b (n=41)	p-value
Total Cholesterol (IQR) mg/dl	78.80 (64.73 to 97.52)	96.50 (80.35 to 121.71)	p < 0.0001
LDL (IQR) mg/dl	1.01 (0.70 to 1.23)	1.13 (0.90 to 1.36)	p < 0.0001
HDL (IQR) mg/dl	0.61 (0.31 to 1.26)	0.82 (0.67 to 1.02)	p < 0.0001
Serum lipase (IQR) mg/dl	9 (7.00 to 11.00)	13 (11.00 to 14.00)	p < 0.0001
Total lipids (IQR) mg/dl	4.05 (3.37 to 4.52)	4.45 (4.20 to 5.23)	P < 0.0001
Group 2	**Group 2a (n=41)**	**Group 2b (n=41)**	**P-value results**
Total Cholesterol (IQR) mg/dl	90.00 (74.26 to 112.90)	102.50 (92.25 to 135.50)	P < 0.0001
LDL (IQR) mg/dl	0.92 (0.765 to 1.32)	1.25 (1.02 to 1.64)	P < 0.0001
HDL (IQR) mg/dl	0.70 (0.59 to 1.17)	0.95 (0.75 to 1.41)	P < 0.0001
Serum lipase (IQR) mg/dl	10 (9.00 to 12.00)	14 (12.00 to 16.00)	P < 0.0001
Total lipids (IQR) mg/dl	4.25 (3.82 to 4.68)	4.8 (4.40 to 5.65)	P < 0.0001

Table 3: Comparison of cholesterol and lipids in both groups from day 1 and day 7 of post-surgical parenteral lipid administration. The p-value of < 0.05 was considered significant.

Parameters	Spearman's coefficient of rank correlation (rho)	95% Confidence Interval for rho	p-value
Total Cholesterol and Total Lipids at the beginning	0.369	0.165 to 0.543	p-value=0.0006
Total Cholesterol and Total Lipids at the end	0.34	0.136 to 0.521	p-value=0.0016
HDL and total lipids at the beginning	0.242	0.0260 to 0.436	p-value=0.0287
HDL and total lipids at the end	0.185	-0.0330 to 0.387	p-value=0.0956
Triglycerides and total lipids at the beginning	0.422	0.226 to 0.585	p-value=0.0001
Triglycerides and total lipids at the end	0.387	0.186 to 0.557	p-value=0.0003
Triglycerides and total lipids at the beginning	0.191	-0.0276 to 0.391	p-value=0.0863
Lipase and Total Lipids association at the end	0.329	0.121 to 0.510	p-value=0.0025
Total lipids and weight at admission	0.246	0.0307 to 0.440	p-value=0.0259
Total lipids and discharge weight	0.164	-0.0575 to 0.371	p-value=0.1453
Triglycerides and weight at admission	0.244	0.0288 to 0.438	p-value=0.0270

Table 4: Associations between values both on day 1 and day 7 of lipid administration. The above table indicates, that if one value decreases or increases, the other is also correlated in the same direction, being slight associations at a rho < 0.2 and moderate between 0.2 and 0.5, respectively strong above 0.5.

Both lots together	Spearman's coefficient of rank correlation (rho)	95% Confidence Interval for rho	p-value
Triglycerides and GA	0.252	0.0375 to 0.445	p-value=0.0221
Triglycerides and DB at the beginning	-0.0601	-0.274 to 0.159	p-value=0.5916
Triglycerides and final DB	0.0300	-0.247 to 0.186	p-value=0.7752
Triglycerides and TB at the beginning	-0.0156	-0.188 to 0.245	p-value=0.7893
Triglycerides and final TB	-0.0156	-0.232 to 0.202	p-value=0.8891
Final total lipids and final DB	-0.00231	-0.219 to 0.215	p-value=0.9835
Total lipids at the beginning and DB at the beginning	-0.0321	-0.247 to 0.186	p-value=0.7749
Total lipids at the end and TB at the end	-0.117	-0.326 to 0.102	p-value=0.2944
Total lipids at the beginning and TB at the beginning	-0.193	-0.393 to 0.0253	p-value=0.0827
Cholesterol and GA	0.210	-0.00688 to 0.409	p-value=0.0577
LDL Cholesterol and GA	0.200	-0.0181 to 0.399	p-value=0.0721
Triglycerides and GA	0.252	0.0375 to 0.445	p-value=0.0221
Total lipids and GA	0.229	0.0130 to 0.425	p-value=0.0382
Cholesterol and weight at admission	0.232	0.0159 to 0.428	p-value=0.0358
Total lipids and weight at admission	0.246	0.0307 to 0.440	p-value=0.0259
Triglycerides and weight at admission	0.244	0.0288 to 0.438	p-value=0.0270
Hospitalization days correlated with GA	-0.613	-0.732 to -0.456	p<0.0001
Total lipids correlated with hospitalization days	-0.231	-0.426 to -0.0144	p-value=0.0371
Triglycerides correlated with hospitalization days	-0.198	-0.398 to 0.0202	p-value=0.0750

Table 5: Comparison of different parameters from both the study groups at the initiation and on the 7th day of lipid administration. The p-value of < 0.05 was considered significant.

The biochemical values were collected on the 7th day of parenteral lipid administration and were further analyzed. (Table 2) Postoperative recovery requires total or partial parenteral nutrition. Parenteral lipid nutrition was initially as 1g/kg/day, with a daily increase of 0.5 g/kg/day until the maximum dose of 3g/kg/day was achieved. Both groups were reevaluated after 7 days. We can see that the total bilirubin (TB) still has an increased value in group 1 (p-value=0.052). No statistical difference between lipase (p-value=0.1198) and total cholesterol (p-value=0.1259) was seen. The total lipids had lower values (p-value=0.0365), and the weight at discharge did not show a statistically significant difference (p-value=0.6063).

Further, comparing the biochemical test results of group 1 newborns, collected on day 1 and day 7 of parenteral lipid administration are presented in table 3. (Table 3) Total cholesterol, LDL, HDL, lipase, and total lipids had much higher values, all being statistically significant (p-value<0.0001).

In the table above (table 5), we can see statistically significant correlations, there are associations on the compared elements. These associations are only noticeable on the combined data. We found that GA correlated with triglycerides and total lipids, both having a moderate positive correlation (p-value=0.0221). In the same way, the weight at admission is associated with the value of total lipids (p-value=0.0259), and triglycerides (p-value=0.0270), and there is also a positive association.

Neonatal complications were monitored during hospitalization in both study groups, such as bronchopulmonary dysplasia (p-value=0.1797), sepsis (p-value=1.0000), necrotizing enterocolitis (NEC) (p-value=0.3993), retinopathy of prematurity (ROP) (p-value=0.3816) and intraventricular hemorrhage (IVH) (p-value=0.7156). There were no statistically significant differences seen among the groups. (Table 1)

Discussion

For neonatal CGIM there was no evidence of advantage of any specific lipid formulation. Various studies have stated that for babies with surgical conditions that are likely to be administered long-term PN, such as those with short or no bowel left, the duration of parenteral nutrition will be much longer than in premature newborns, necessitating proper management by a multidisciplinary team, including a gastroenterologist [20]. It may be more beneficial to use fish oil containing lipid emulsions in babies requiring longer periods of PN, as there is a greater risk of developing PNALD in such circumstances. Nevertheless, a larger number of studies are required to prove this hypothesis [37]. There are different theories regarding the initial quantity to be administered of lipid emulsions, however, the initial dose of 1 g/kg/day was found to be well tolerated in most of the clinical trials. If increment is done gradually by an increase of 0.5 to 1.0 g/kg/day, monitoring for potential adverse effects such as hypertriglyceridemia becomes mandatory [31]. In our study, no such side effects were noticed, and TG levels were within normal limits even after 7 days of IV lipid administration.

Intravenous lipid emulsions (IVLEs) vary for infant use. Soybean oil is the main component of traditional lipid emulsions. These emulsions nowadays have a wide variety of other oil sources (olive, coconut, and fish oil). Soybean oil-based emulsion (e.g. Intralipid) is comparatively rich in essential n-6 (linoleic) and n-3 (alpha-linolenic) polyunsaturated fatty acids, involved in IFALD pathogenesis, non-nutritive phytosterols, pro-inflammatory properties but are capable of contributing to liver damage, without DHA or EPA, and with potential for brain and retinal development

damage [38]. Based on the previous studies we find it vital to have a close watch on all surgical neonates receiving mixed oil lipid emulsions [39].

A combination of soybean, medium chain triglycerides, olives, and Fish oil emulsions (e.g. SMOFlipid), usually contain higher n-3 polyunsaturated fatty acids, including lower DHA and EPA phytosterols in comparison to IntraLipid [40]. Fish oil emulsion (e.g. Omegaven), contains less amount of essential fatty acids than IntraLipid and SMOFlipid and is suitable for preventing essential FA deficiency despite these lower levels, but DHA, EPA is in higher quantity than in IntraLipid and SMOFlipid [41].

In general, it can be stated that the IVLEs are well tolerated. While, on the other hand, there are no reports on the overall clinical benefits for any specific IVLE in neonates [42]. In clinical practice, there are important outcomes including mortality, growth, chronic lung disease, sepsis, severe ROP ⩾ stage 3, and cholestasis by using any specific preparations in newborns [43,44]. Water and fat-soluble vitamins are usually added to the lipid emulsion. While in our study, we found no cholestasis, nor there any mortality noticed.

Almost all the emulsions with additional fat and water-soluble vitamins are made in order to provide 1 g of lipid (SMOFlipid or ClicOleic) in 6 mL of lipid emulsion with vitamins (Soluvit N and Vitalipid N Infant). Hence, a 1 gram of lipid/kg/day equates to 6 mL lipid emulsion with vitamins/kg/d, which equates to an energy intake of 10 kcal/kg/day [31]. Although, how much should be the starting dose of these products still remains unclear and requires more in-depth studies. The lipid emulsions contain 80% water (6 mL lipid emulsion with vitamins containing 5 mL water; 12 mL lipid emulsion with vitamins contains 10 mL water; 18 mL lipid emulsion with vitamins containing 15 mL water) [45]. However, we propose to include the water content of lipid infusions in the total fluid intake, being equal to 15 ml/kg/day of water when the total quantity of lipid intake reaches to 3 g/kg/day as in our study. Studies have demonstrated that when a mixture of SMOFlipid and medium-chain triglycerides (MCT) /long-chain triglycerides (LCT) are more hepato-protective [46]. Similarly, a study conducted by Hanindita M.H. et al, demonstrated that when such mixtures are given the leucocyte count ω-6, and C-reactive protein levels do not increase as seen in non-mixed individual lipid emulsions [47].

In our study, we found that there were no adverse effects if the lipids were initiated at an early stage. Since it is not always possible to obtain optimal and recommended nutrition, based on the complexity of the day-to-day management of operated neonates [48], proper guidelines can help.

PN administration requires careful monitoring. In the case of high-risk newborns, it is mandatory to take into account a few aspects related to biochemical monitoring. Some of these include collecting the minimum blood volume needed for the tests, using a protocol agreed upon with the local clinical laboratory to retrieve as much information as possible from the sample, and coordinating the timing of blood tests to minimize the number of blood samples needed. Keeping this important parameter in mind, we never exceeded in our study a total of 2 ml of blood sample for running the test per day. Serious and unexpected biochemical instability because of PN is rare but can be potentially fatal. With every 1g/kg/day increase of lipids and every week after reaching the higher dosages of >3g/kg/day monitoring should be done more vigorously, especially of the triglyceride (TG) levels [7,8]. In our study, we increased just 0.5 g/kg/day of lipids, and the maximum dose was never let to cross 3 g/kg/day. On administration of high lipid doses (>3 g/kg/day), frequent monitoring is required in critically unwell cases e.g. with sepsis [49]. Due to high levels of lipids, the risk of developing ASCVD increases later in life.

In infants having VLBW, the LE administration of MCT/ω-3-PUFA-containing substances proves to be beneficial in attaining a better lipoprotein profile. A lower incidence of cholestasis was observed, a preventive effect of MCT/ω-3-PUFA-containing LE on parenteral nutrition-associated cholestasis still is questionable [50]. Low dosing of soy-based IV lipid emulsion helps to reduce the fast increase in direct bilirubin compared to when given in higher dosages [51].

Few studies have focused on this special population of congenital malformations; therefore, further studies are required to improve the nutritional approach and the management of long-term consequences in these newborns.

Limitations in our Study:

1. One of the major limitations of the study is that the total number of patients included were just 82. Drawing firm conclusions requires larger cohort studies.
2. Since long-term effects of early initiation of lipids during the initial days of surgery are hard to quantify.
3. Neonates having other associated pathologies sometimes make it difficult to evaluate the benefits or disadvantages of a prescribed nutritional plan. Similarly, in our study having a group of neonates suffering just from CGIM was difficult to find, and some had other pathologies as well, which might influence the results.

Lipid parenteral nutrition plays a crucial role in the management of neonates that are recently operated for various gastrointestinal malformations, both during the intervention and after the operation. National and international guidelines should be thoroughly consulted, and decisions of initiation and dosing of parenteral nutrition should be made on a case-to-case basis to provide accurate tailor-made plans. The provision of macronutrients and micronutrients should be planned according to the current knowledge and international recommendations. Lipid deficiency and overload should be routinely monitored. In addition, clinical and biochemical signs of PN and surgery-related morbidities, and growth failure, should be carefully assessed. No adverse effects were documented if parenteral lipid emulsions are initiated at an early phase postoperatively in congenital gastrointestinal malformations.

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Institutional Review Board Statement and Informed Consent Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee for Scientific Research and Development of the "Louis Tourcanu" Children's Emergency Clinical Hospital Timișoara (PRM/453/6.07.2023 reg. no. 10594/06.07.2023). Informed consent has been granted by the parents and legal guardians of all neonates enrolled in this study.

Author Contributions

T. B.: study design, writing the initial draft, data curation. A. M. M. and A.B.: data curation. M. B.: study design and validation of results. D.N.: statistical analysis M.C.P.: drawing conclusions, supervision, validation of results, N. R. K. and A.B.: conceptualization, writing and revising the manuscript, data validation.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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