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Relationship between the Effects of Different Parenteral Nutrition Durations of Two Intravenous Fat Emulsions on Intravenous Nutrition-related Immune Status and Clinical Outcomes in Premature Infants

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ABSTRACT

Premature infants with immature gastrointestinal tracts rely on parenteral nutrition (PN) to meet nutritional and energy requirements for growth. In this study, we compared the nutrition-related immune status of premature infants receiving SMOF emulsions (multiple oil-fat emulsions) versus those receiving MCT/LCT emulsions (medium-/long-chain triglyceride emulsions) at different times during PN, and we analyzed the relationship between immune function and clinical outcomes.

Sixty premature infants from Dongxihu District People's Hospital, recruited between September 2023 and September 2024, were divided into an observation group and a control group. The observation group received SMOF emulsions, while the control group received MCT/LCT-containing emulsions. We compared immune function, clinical outcomes, and complications between the two groups at different PN timings. The effects of fat-emulsion type on immune indices and their relationship with clinical outcomes were assessed using logistic regression and ROC analysis.

The clinical data of the preterm infants in both groups were similar. Immune function and clinical outcomes were better in the observation group than in the control group, and the complication rate was lower. Logistic and ROC analyses revealed that the type of fat emulsion was closely related to immune indices, and these immune indices were highly correlated with clinical outcomes.

Both interventions improved immunity in preterm infants, with better results in the observation group than in the control group. The use of SMOF emulsions was superior to MCT/LCT-containing emulsions in preterm infants requiring long-term PN, and this immune improvement significantly optimizes clinical outcomes.

Keywords: Fat emulsion; Immunity; Outcome assessment; Parenteral nutrition; Premature

INTRODUCTION

Infants born alive prior to 37 weeks of gestational age is collectively referred to as premature infants. Premature infants have significantly poorer organ function and adaptive capacity than full-term infants do, especially those with lower birth weights.[1] Delayed food intake by premature infants is not conducive to intestinal

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maturation, and the development of digestive and absorptive functions is not ensured, which in the long term can lead to neurobehavioral developmental abnormalities and have an impact on the immune function of the body.[2] Compared with full-term infants, premature infants' enteric nervous system development lags behind, and small intestinal dyskinesia leads to impaired absorption of nutrients. In recent years, medical development has been rapid, and the technology of preterm pediatric intensive care has improved, which can provide more suitable survival conditions for premature infants and safeguard their extrauterine growth. In preterm intensive care units, the use of antimicrobial drugs, the lack of breastfeeding, and medical operations have adverse effects on the feeding of premature infants and their growth and development.[3]

With the increase in the proportion of critically premature infants and the improvement in their level of care in recent years, the use of parenteral nutrition (PN) for premature infants has increased, but most premature infants have difficulty tolerating gastrointestinal nutrition after birth. Therefore, PN has gradually become one of the key reasons for the increased success rate of treatment of premature infants.[4] As the duration and total amount of PN use increase, the incidence of PN-related adverse conditions also increases accordingly.

Fat emulsions can provide premature infants with highly concentrated calories and essential fatty acids.[5] However, because of their immature intestinal mucosal barrier function, liver function, and immune system, premature infants have insufficient capacity for bile salt uptake and intestinal lumen utilization, and an excessive parenteral nutritional supply may lead to complications such as hepatic steatosis, hyperlipidemia, and cholestasis.[6] Thus, how to safely administer PN has gradually become an important research direction for preterm pediatricians.

Intravenous fat emulsions, an essential component of PN for premature infants, provide a high concentration of calories and, in premature infants who are not yet receiving gastrointestinal nutrition, provide the body with a concentrated source of noncarbohydrate energy, including essential fatty acids (EFAs) and polyunsaturated fatty acids (PUFAs).[7] The use of intravenous fat emulsions in PN reduces the body's dependence on glucose as the main nonprotein energy source and prevents adverse clinical outcomes caused by EFA deficiency.[8] Fat emulsions can be classified into multiple-oil fat emulsions (SMOFs) and medium- and long-chain fat emulsions (MCT/LCTs) on the basis of the composition of their oil phase.[9] Early fat emulsions were dominated by soybean oil fat emulsions, but they contain phytosterols and omega-6 fatty acids, which can lead to cholestasis in premature infants, which severely affects their liver function.[10] In recent years, with the development of science and technology, SMOF, which is a mixture of soybean oil, medium-chain fat, olive oil, fish oil, and vitamin E, has been gradually used in clinical practice. SMOF contains α-tocopherol, with a balanced proportion of omega-6 fatty acids over omega-3 fatty acids, and it has the effects of anti-lipid peroxidation and blocking excessive inflammatory responses.[11] Studies have shown that intravenous fat emulsions are immunomodulatory and contain high levels of antioxidants, thus reducing the risk of oxidative stress injury as well as complications. Premature infants have limited antioxidant capacity and are highly susceptible to oxidative stress-induced infections and inflammatory responses, which can lead to the onset and development of many serious diseases.[12]

Although there are preliminary reports on the clinical application of SMOF and MCT/LCT in PN for preterm infants, most of the studies focus on the short-term nutritional effects and lack systematic analyses of the immune function and the risk of complications in different PN durations. Previous studies have mostly explored the metabolic effects of fat emulsions alone, neglecting their regulatory mechanisms on the immune network of preterm infants. In particular, the dynamic associations between immune indicators and clinical outcomes at different PN durations have not yet been fully elucidated, which is a key gap in the clinical decision-making for preterm infants on long-term PN. Therefore, the present study systematically evaluated the effects of fat emulsion type on the immunity and clinical outcomes of preterm infants on long-term PN by comparing the immune status changes of SMOF and MCT/LCT under different PN durations and combining receiver operating characteristic (ROC) curve analysis of immune indexes and clinical outcomes, with the aim of filling the above research gaps and providing a scientific basis for the formulation of precise clinical nutritional protocols.

MATERIALS AND METHODS

Research Design

The aim of this study was to systematically compare the

changes in nutrition-related immune status of two fat emulsions, SMOF and MCT/LCT, applied to preterm infants at different PN durations (PN duration was categorized as 15–21 days, 22–28 days, and ≥29 days according to the study of Lin et al[9]) and to further assess their dynamic associations on immune function and clinical outcomes of preterm infants by detecting immunoglobulins and immune factors. The study was a single-center retrospective cohort study with strict ethical review criteria. Sixty preterm infants admitted to the Preterm Infant Care Unit of Dongxihu District People's Hospital from September 2023 to September 2024 were selected as the study subjects and were divided into an observation group (SMOF injection) and a control group (MCT/LCT-containing injections) according to the different choices of fat emulsions in their clinical treatment protocols, with 30 cases in each group. The flowchart of this study is presented in Figure 1.

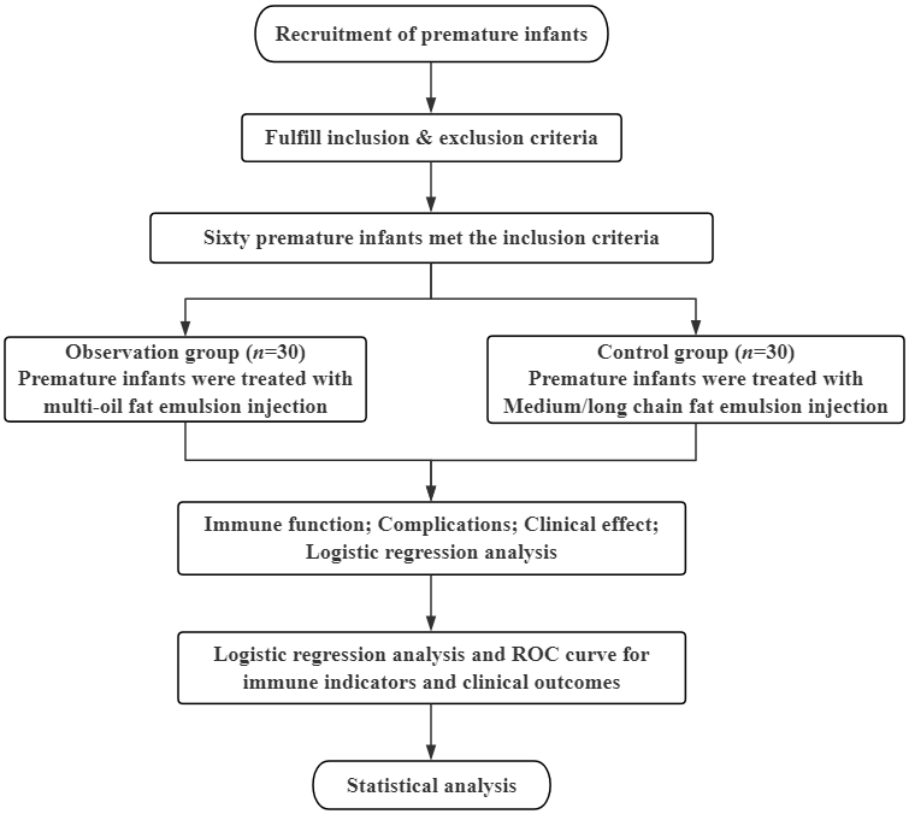

Figure 1. Flowchart

Randomization and Blinding

In this study, 60 preterm infants were enrolled in a clinical diagnostic trial. They were assigned to observation and control groups based on their different choices of fat emulsion in their clinical treatment regimen. Patients and treating physicians could not be blinded to the intervention during treatment; however, study staff and data analysts were blinded to treatment allocation.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) no missing case data and admission within 24 hours of birth; (2) gestational age <34 weeks or birth weight <1500 g; (3) PN was initiated within 48 hours postnatally and lasted >14 days; and (4) the informed consent form was signed by family members or guardians.

The exclusion criteria were as follows: (1) congenital intrauterine infections; (2) congenital malformations or inherited metabolic diseases; (3) maternal or infant hemolytic disease with incompatible blood groups; and (4) inborn genetic metabolic diseases.

Nutrition Protocol

Nutritional management of all study subjects followed the Chinese Guidelines for the Clinical

Application of Neonatal Nutritional Support.[13] PN preparation was maintained at a uniform rate for 24 hours through a central vein via a micropump. SMOF (100-mL specification; Fresenius Kabi Austria GmbH) was applied to the observation group; MCT/LCT-containing injections (500 mL:50 g specification; Huarui Pharmaceutical Co, Ltd, China) were applied to the control group. The starting dose of fat emulsion was 1 g/kg/d, which was increased by 0.5 to 1.0 g/kg/d and gradually increased to 3.0 to 3.5 g/kg/d. The starting dose of amino acids ranged from 1 to 2 g/kg/d and was gradually increased to 3 to 4 g/kg/d. The glucose (100 mL:10 g specification; Shiyao Group, China) dosage started at an infusion rate of 4 to 8 mg/kg/min and was gradually increased on the basis of the glucose tolerance level, reaching a maximum of 11 to 14 mg/kg/min. Breastfeeding began as early as possible after birth, and breast milk was preferred. Breastfeeding was defined as breastfeeding more than 50% of total enteral feeds. When the amount of enteral feeding increased, the amount of PN decreased accordingly. PN was discontinued once enteral feeds were 130 to 150 mL/kg/d, and the time from the start of enteral feeds until total enteral feeds reached 150 mL/kg/d was the time to reach total enteral nutrition. Measurements were taken before PN initiation and at 15–21 days, 22–28 days, and ≥29 days after PN initiation.

Observation Indicators

Immune Indicators

The two groups of premature infants were observed for immune index indicators.[14] First, 5 mL of venous blood was drawn from the elbow in the morning on an empty stomach and centrifuged at 3000 rpm for 10 minutes for processing, and the supernatant was collected after serum separation. Then, the serum sample was tested by the laboratory department of our hospital uniformly via the enzyme-linked immunosorbent assay (ELISA) method, and the levels of the patients' serum test indices were recorded after treatment. Serum immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin G (IgG) levels were analyzed with a human IgA ELISA kit (D711189-0096; Sangon Biotech, China), a human IgM ELISA kit (ab214568; Abcam Plc, Britain), and a human IgG ELISA kit (D711074-0096; Sangon Biotech, China).

Flow cytometry (BriCyte E6; Shenzhen Myriad Bio-Medical Electronics, China) was used to detect the percentage of $CD4^+$ and $CD8^+$ T cells in both groups of preterm infants.[15] Anticoagulated whole blood samples were taken, and fluorescent staining was performed after adding erythrocyte lysate to remove erythrocytes. Subsequently, cells were washed twice with phosphate-buffered saline (PBS) to remove unbound antibodies. Finally, the treated cell suspension was placed in a flow cytometer, and the proportion of $CD4^+$ and $CD8^+$ T cells in it was analyzed and recorded.

Complication Rate

(1) Parenteral nutrition–associated cholestasis (PNAC): The presence of yellow skin staining and/or light-colored stools; direct bilirubin ≥34 μmol/L or total bilirubin less than 85 μmol/L; and the exclusion of causes such as viral, bacterial, or fungal infections and biliary developmental malformations.[16]

(2) Bronchopulmonary dysplasia (BPD): Premature infants were continuously oxygen dependent for more than 28 days after birth and were graded on the basis of a corrected fetal age of 36 weeks or an oxygen requirement at discharge. Moderate was defined as an oxygen concentration of 21% to 30%, and severe was defined as an oxygen concentration of more than 30% or requiring orthostatic or mechanical ventilation.[17]

(3) Diagnostic criteria for diseases such as late-onset sepsis (LOS), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP) were based on the relevant literature or clinical guidelines.[18,19]

Clinical Efficacy

The clinical efficacy of the two groups of premature infants was determined as follows.[20] **Marked effect:** the relevant clinical symptoms basically disappeared after treatment, and there were no seizures within 3 months after treatment. **Effective:** the relevant clinical symptoms were significantly reduced after treatment, and the number of recurrences was significantly reduced. **Ineffective:** no change in the clinical symptoms or the number of seizures, or even a tendency to worsen.

Statistical Analysis

The data were analyzed via SPSS version 27.0. Flowcharts were drawn using Lucidchart. The data that conformed to a normal distribution are presented as mean ± (SD), and comparisons among groups were performed with independent samples *t* tests. The count data are expressed as rates (%) and compared using χ^2 tests, with $p < 0.05$ indicating that the difference was

statistically significant. Logistic regression trend analysis was used to explore the effects of fat emulsion type on immune markers and their relationships with clinical outcomes, and the associations and closeness of immune markers with clinical outcomes in premature infants under the optimal regimen were assessed via ROC curves and the area under the curve (AUC).

RESULTS

Baseline Characteristics

The baseline demographic characteristics and baseline status of patients randomly assigned to the control and observation groups are presented in Table 1. No remarkable discrepancies between the groups were observed in terms of demographic variables, instruments, or status ($p > 0.05$). Thus, the randomization process achieved the important goal of evenly assigning participants to the two groups; the two groups were comparable at the pretreatment level, and confounding by demographic or clinical factors did not affect the analysis of treatment outcomes.

Immune Indicators

A comparison of immune indicators between the two groups of premature infants is shown in Tables 2 to 7. Before treatment, no marked differences were found in the IgA, IgM, and IgG immune indicators; the percentages of $CD4^+$ T cells and $CD8^+$ T cells; or the $CD4^+/CD8^+$ ratio ($p > 0.05$). The immunological indices of premature infants in both groups changed with increasing PN duration. The IgA, IgM, and IgG contents; the percentage of $CD4^+$ T cells; and the $CD4^+/CD8^+$ ratio increased significantly with increasing PN duration and were highest at PN durations ≥29 days ($p < 0.05$). The IgA, IgM, and IgG levels; the percentage of $CD4^+$ T cells; and the $CD4^+/CD8^+$ ratio of premature infants in the observation group were greater than those in the control group at different PN durations ($p < 0.05$). The percentage of $CD8^+$ T cells in both groups of premature infants decreased markedly with increasing PN duration, and the percentage in the observation group was lower than that in the control group during this process ($p < 0.05$).

Table 1. Baseline characteristics of patients in each group

Parameter	Control group (n = 30), mean (SD)	Observation group (n = 30), mean (SD)	t/χ^2	p
Gestational age, wk	29.92 (1.31)	30.12 (1.16)	0.626	0.534
Birth weight, g	1295.14 (80.96)	1299.24 (80.53)	0.197	0.845
Head circumference, cm	26.47 (0.95)	26.34 (0.96)	−0.527	0.600
Body length, cm	36.42 (0.88)	36.50 (0.96)	0.336	0.738
No. (%)				
Sex (male/female)	16/14	15/15	0.067	0.796
Premature rupture of membranes >18 h	5/25	6/24	0.111	0.739
Cesarean/vaginal delivery	21/9	22/8	0.082	0.774
Gestational hypertension	10/20	9/21	0.077	0.781
Gestational diabetes	11/19	10/20	0.073	0.787
Perinatal infection in mother	25/5	26/4	0.131	0.718
Advanced maternal age	23/7	22/8	0.089	0.766
Mean (SD)				

The percentage of $CD8^+$ T cells in both groups of premature infants decreased markedly with increasing PN time, and the percentage in the observation group was lower than that in the control group during this process ($p<0.05$). The results showed that with the increase in the duration of parenteral nutrition, the immune function of

preterm infants in the observation group was significantly better than that of the control group. This suggests that in clinical practice, for preterm infants requiring long-term PN, the selection of SMOF injection can more effectively improve the immune function and reduce the risk of infection and other complications, which provides an important basis for optimizing the nutritional support program for preterm infants.

Table 2. Changes in IgA levels before and after treatment

PN duration	Control group, mean (SD), g/L	Observation group, mean (SD), g/L	*t*	*p*
Pretreatment	0.18 (0.02)	0.17 (0.02)	−1.936	0.058
15–21 d	0.20 (0.01)[a]	0.23 (0.03)[a]	5.196	<0.001
22–28 d	0.22 (0.02)[a,b]	0.30 (0.03)[a,b]	12.153	<0.001
≥29 d	0.25 (0.03)[a,b,c]	0.41 (0.03)[a,b,c]	20.656	<0.001

[a]Significant difference from pretreatment ($p < 0.05$).
[b]Significant difference from 15–21 d ($p < 0.05$).
[c]Significant difference from 22–28 d ($p < 0.05$).

Table 3. Changes in IgM levels before and after treatment

PN duration	Control group, mean (SD), g/L	Observation group, mean (SD), g/L	*t*	*p*
Pretreatment	0.28 (0.06)	0.29 (0.05)	0.701	0.486
15–21 d	0.33 (0.04)[a]	0.36 (0.05)[a]	2.566	<0.05
22–28 d	0.36 (0.04)[a,b]	0.42 (0.03)[a,b]	5.715	<0.001
≥29 d	0.39 (0.05)[a,b,c]	0.50 (0.06)[a,b,c]	7.714	<0.001

[a]Significant difference from pretreatment ($p < 0.05$).
[b]Significant difference from 15–21 d ($p < 0.05$).
[c]Significant difference from 22–28 d ($p < 0.05$).

Table 4. Changes in IgG levels before and after treatment

PN duration	Control group, mean (SD), g/L	Observation group, mean (SD), g/L	*t*	*p*
Pretreatment	6.03 (0.27)	5.96 (0.24)	−1.061	0.293
15–21 d	6.30 (0.24)[a]	6.55 (0.34)[a]	3.290	<0.05
22–28 d	6.61 (0.45)[a,b]	7.38 (0.42)[a,b]	6.852	<0.001
≥29 d	7.02 (0.33)[a,b,c]	8.48 (0.59)[a,b,c]	11.829	<0.001

[a]Significant difference from pretreatment ($p < 0.05$).
[b]Significant difference from 15–21 d ($p < 0.05$).
[c]Significant difference from 22–28 d ($p < 0.05$).

Table 5. Change in percentage of $CD4^+$ T cells before and after treatment

PN duration	Control group, mean (SD), %	Observation group, mean (SD), %	*t*	*p*
Pretreatment	32.21 (1.21)	32.63 (1.27)	1.311	0.195
15–21 d	34.34 (1.01)[a]	35.05 (1.06)[a]	2.656	<0.05
22–28 d	35.85 (1.28)[a,b]	37.54 (1.95)[a,b]	3.968	<0.001
≥29 d	37.86 (1.63)[a,b,c]	40.31 (1.34)[a,b,c]	6.360	<0.001

[a]Significant difference from pretreatment ($p < 0.05$).
[b]Significant difference from 15–21 d ($p < 0.05$).
[c]Significant difference from 22–28 d ($p < 0.05$).

Table 6. Changes in the percentage of CD8+ T cells before and after treatment

PN duration	Control group, mean (SD), %	Observation group, mean (SD), %	*t*	*p*
Pretreatment	26.62 (0.78)	26.73 (0.75)	0.557	0.580
15–21 d	25.47 (0.86)[a]	24.61 (1.12)[a]	−3.336	<0.05
22–28 d	23.66 (1.24)[a,b]	22.22 (1.05)[a,b]	−4.854	<0.001
≥29 d	21.58 (1.36)[a,b,c]	19.87 (1.27)[a,b,c]	−5.033	<0.001

[a]Significant difference from pretreatment ($p < 0.05$).
[b]Significant difference from 15–21 d ($p < 0.05$).
[c]Significant difference from 22–28 d ($p < 0.05$).

Table 7. Change in $CD4^+/CD8^+$ Ratio Before and After Treatment

PN duration	Control group, mean (SD)	Observation group, mean (SD)	*t*	*p*
Pretreatment	1.30 (0.04)	1.29 (0.04)	−0.968	0.337
15–21 d	1.45 (0.02)[a]	1.51 (0.04)[a]	7.348	<0.001
22–28 d	1.57 (0.04)[a,b]	1.69 (0.06)[a,b]	9.115	<0.001
≥29 d	1.67 (0.06)[a,b,c]	1.97 (0.07)[a,b,c]	17.823	<0.001

[a]Significant difference from pretreatment ($p < 0.05$).
[b]Significant difference from 15–21 d ($p < 0.05$).
[c]Significant difference from 22–28 d ($p < 0.05$).

Complications

The complications of premature infants in both groups are presented in Table 8. No remarkable discrepancy was found in the prevalence of PNAC, BPD, LOS, NEC, or ROP in either group ($p > 0.05$). The incidence of total complications in premature infants in the observation group was 26.7% (8 of 30), markedly lower than that in the control group (46.7% [14 of 30]), which was a statistically significant difference ($p = 0.003$). These findings indicate that SMOF injection can reduce the total complication rate of premature infants.

In the context of clinical practice, the results of this study have clear clinical translational implications. The $CD4^+/CD8^+$ ratio in the observation group continued to increase with prolonged PN (especially at ≥29 days), and the improvement of this immune indicator was directly related to the reduction of clinical infection complications. Because the elevated $CD4^+/CD8^+$ ratio suggests an optimised ratio of Th cells to Tc cells, the immune response of preterm infants can be enhanced. Meanwhile, the levels of IgA, IgG, and IgM in the observation group increased more significantly with the time of PN, in which IgA, as a key factor of mucosal immunity, could enhance the function of mucosal barriers such as the intestines, and IgG could neutralise toxins through humoral immunity, which synergistically led to a significant reduction in the rate of PN-associated infections in the observation group compared with that in the control group. This also confirms that SMOF significantly reduces the risk of infection during PN in preterm infants by regulating the balance of T cell subpopulations and enhancing humoral and mucosal immunity.

Table 8. Complication rates

Complication	Control group, No. (%)	Observation group, No. (%)	χ^2	*p*
PNAC	3 (10.0)	2 (6.7)	0.579	0.447
BPD	2 (6.7)	1 (3.3)	1.684	0.194
LOS	4 (13.3)	3 (10.0)	0.442	0.506
NEC	4 (13.3)	2 (6.7)	2.000	0.157
ROP	1 (3.3)	0 (0.0)	3.046	0.081
Total incidence	**14 (46.7)**	**8 (26.7)**	**8.580**	**0.003**

Clinical Efficacy

The results of the clinical efficacy analysis of premature infants in both groups are presented in Table 9. The total effective rate of treatment in the control group was 83.3% (25 of 30) and that in the observation group was 93.3% (28 of 30), markedly greater than that in the control group. The difference was statistically significant ($p < 0.05$), which indicated that the efficacy in the observation group was greater.

Effects of Fat Emulsion Type on Clinical Outcomes

The effects of the fat emulsion type on the immune indicators of premature infants were analyzed in a binary logistic regression model by using the fat emulsion type (assigned value: 0 for SMOF, 1 for MCT/LCT) as the independent variable and complications (0 for not occurring, 1 for occurring), clinical efficacy (0 for significant, 1 for ineffective), and expression of immune indicators (0 for positive, 1 for negative) as the dependent variables. The results are presented in Table 10, which shows that a significant correlation exists between the type of fatty emulsion and the improvement of immune indicators in premature infants. The type of fatty emulsion had a positive influence on the change in immune indicators, meaning that for every 1-unit increase in the category, the odds of improved immune indicators increased by a factor of 4.181. The type of fat emulsion had a significant and independent effect on complications in premature infants, meaning that for every unit increase in this category, the odds of complications increased by a factor of 4.009. The type of fat emulsion was significantly and positively correlated with the clinical outcomes of premature infants, meaning that for every unit increase in this category, the odds of effective clinical outcomes increased by a factor of 3.671.

Impact of Immune Indicators on Clinical Outcomes

The results of the logistic regression analysis of the effects of immune indicators on clinical outcomes are shown in Tables 11 and 12, which revealed significant correlations between the effects of immune proteins (IgA, IgM, and IgG) and immune factors (percentages of $CD4^+$ T cells, $CD8^+$ T cells, and $CD4^+/CD8^+$ ratio) on clinical outcomes ($p < 0.05$).

Table 9. Clinical efficacy analysis

Group	Marked effect, No.	Effective, No.	Ineffective, No.	Total effective rate, No. (%)
Control group	14	11	6	25 (83.3)
Observation group	15	13	2	28 (93.3)
χ^2				
p value				

Table 10. Logistic regression analysis of fat emulsion type on clinical outcomes

Variables	Regression coefficient	SE	Wald value	*p*	OR (95% CI)
Immune indicators	1.430	0.606	5.564	0.018	4.181 (1.274–13.722)
Complications	1.389	0.665	4.357	0.037	4.009 (1.088–14.770)
Clinical efficacy	1.300	0.626	4.311	0.038	3.671 (1.076–12.530)

Table 11. Logistic regression analysis of immune proteins on clinical outcomes

Variable	Regression coefficient	SE	Wald value	*p*	OR (95% CI)
IgA	1.440	0.600	5.763	0.016	4.219 (1.302–13.667)
IgM	1.302	0.637	4.184	0.041	3.678 (1.056–12.809)
IgG	1.184	0.599	3.907	0.048	3.268 (1.010–10.572)

Table 12. Logistic Regression Analysis of Immune Factors on Clinical Outcomes

Variable	Regression coefficient	SE	Wald value	*p*	OR (95% CI)
$CD4^+$ T cells	1.253	0.609	4.234	0.040	3.501 (1.061–11.550)
$CD8^+$ T cells	1.403	0.639	4.821	0.028	4.066 (1.163–14.219)
$CD4^+/CD8^+$	1.295	0.597	4.711	0.030	3.650 (1.134–11.752)

ROC Curve Analysis

The results of the ROC curve analysis are presented in Table 13 and Figure 2, which show that immune indicators were strongly associated with clinical outcomes in premature infants ($p < 0.05$). The AUCs for immune proteins were as follows: IgA, 0.761; IgG, 0.746; and IgM, 0.708. The AUCs for immune factors were as follows: $CD4^+$ T cells, 0.730; $CD4^+/CD8^+$, 0.677; and $CD8^+$ T cells, 0.664.

Table 13. ROC curve analysis of immune indicators on clinical outcomes

Variable	AUC	SE	*p*	95% CI
IgA	0.761	0.063	0.001	0.639–0.884
IgM	0.708	0.069	0.006	0.572–0.844
IgG	0.746	0.065	0.001	0.617–0.874
$CD4^+$ T cells	0.730	0.065	0.002	0.604–0.856
$CD8^+$ T cells	0.664	0.071	0.029	0.526–0.803
$CD4^+/CD8^+$	0.677	0.069	0.019	0.541–0.813

AUC: area under the curve; ROC: receiver operating characteristic.

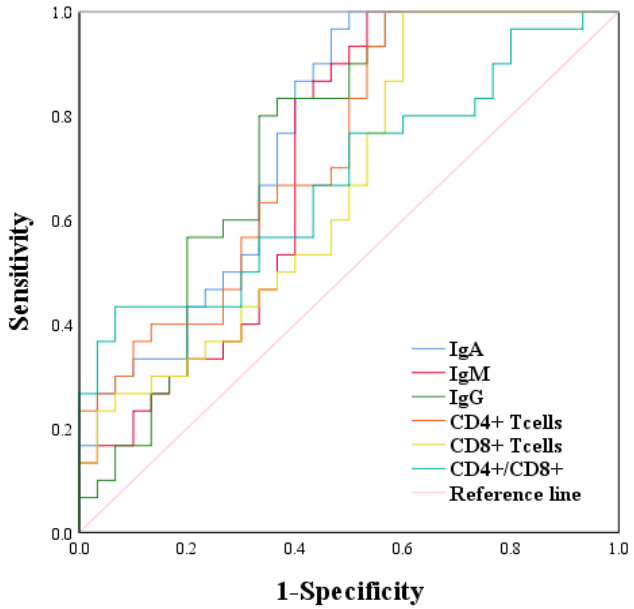

Figure 2. ROC curves of immune indicators on clinical outcomes.

DISCUSSION

The survival rate of premature infants has increased remarkably with the development of perinatal medicine and preterm diagnostic and treatment techniques. Premature infants usually cannot tolerate enteral feeding or do not tolerate it fully due to incomplete development or certain pathologies, and PN is considered a short-term transitional means of saving premature infants. It is used to provide nutritional support until complete enteral nutrition can be implemented.[21] PN consists of macronutrients (ie, glucose, fat emulsion, protein) and micronutrients (eg, calcium, potassium), with fat emulsion being a key component of PN, providing an important source of energy and a rich source of EFAs, such as linoleic and α-linolenic acids. These fatty acids are precursors of eicosanoids required for platelet function, the immune response, inflammation, and early visual and neurological development.[22] Effective feeding practices for premature infants promote weight recovery, and early establishment of PN measures is more favorable for growth and development.

SMOF, including olive oil and soybean oil, is rich in monounsaturated fatty acids and has more α-tocopherol than MCT/LCT, which can maintain the immune function of the body and reduce inflammatory reactions. In addition, SMOF has a much higher α-tocopherol content than other fat emulsions do, which makes it

more suitable for critically ill premature infants, especially those with severe infections, jaundice, and severe lung disease.[23,24] MCT/LCT is a physical blend of long-chain triglycerides with medium-chain triglycerides, the main component of which is coconut oil. It has increased solubility compared with long-chain fat emulsions, is more easily cleared by oxidation, and does not affect hepatic function. In addition, it has a reduced omega-6 polyunsaturated fatty acid content and an attenuated risk of immunosuppression compared with long-chain fat emulsions and is therefore better suited for premature infants with poor hepatic function or the presence of immunosuppression.[25]

Immune function is an important indicator for assessing the growth and developmental status of premature infants, and the effective establishment of an autonomous immune function barrier can play an inhibitory role in the prevention of infections in premature infants. A good state of the immune system is more conducive to the resistance of premature infants to infections, which for a variety of diseases can play a preventive role.[26] The types of lipid emulsions used for PN in premature infants in the clinic have evolved over time, and the present study further analyzed the relationships between immune indicators and clinical outcomes by comparing the changes in immune indicators and clinical outcomes in premature infants after receiving SMOF or MCT/LCT for different periods. Previous studies have shown that receiving lipid emulsion for at least 7 to 14 days has an effect on biochemical indicators in infants, which is presumed to be a sufficient time period to have a meaningful effect on clinical outcomes. In contrast, the comparison in this study revealed that during PN, while immune indicators improved in both groups of premature infants, in the observation group, the levels of the immune proteins IgA, IgM, and IgG; the percentage of the immune factor $CD4^+$ T cells; and the $CD4^+/CD8^+$ ratio were greater, while the percentage of $CD8^+$ T cells was lower than in the control group. The results revealed that with an increasing duration of PN, the immune indices of premature infants in the observation group were significantly better than those in the control group, indicating that SMOF injection applied to premature infants in the observation group could significantly improve the immunity of premature infants and that the immune indices reached the optimal values when the duration of PN was≥29 days.

In the context of clinical practice, the results of this study have clear clinical translational implications. The $CD4^+/CD8^+$ ratio in the observation group continued to increase with prolonged PN (especially at≥29 days), and the improvement of this immune indicator was directly related to the reduction of clinical infection complications. Because the elevated $CD4^+/CD8^+$ ratio suggests an optimized ratio of helper T cells to cytotoxic T cells, the immune response of preterm infants can be enhanced. Meanwhile, the levels of IgA, IgG, and IgM in the observation group increased more significantly with the duration of PN. IgA, as a key factor of mucosal immunity, could enhance the function of mucosal barriers such as the intestines, and IgG could neutralize toxins through humoral immunity, which synergistically led to a significant reduction in the rate of PN-associated infections in the observation group compared with that in the control group. This also confirms that SMOF significantly reduces the risk of infection during PN in preterm infants by regulating the balance of T-cell subpopulations and enhancing humoral and mucosal immunity.

The results of the present study revealed that after the duration of PN was ≥29 days, the total complication rate of premature infants in the observation group was lower than that of the control group, whereas the clinical efficacy was greater than that of the control group, which indicated that the SMOF intravenous solution used in premature infants in the observation group was significantly better than the MCT/LCT intravenous solution. The study results indicated that no marked discrepancy in the incidence of PNAC, BPD, LOS, NEC, or ROP was found in either group of premature infants. This may be due to the limitation of the duration of PN treatment; infants with a PN duration≥29 days accounted for only 35% of the total sample in this study, and complications such as PNAC and BPD are often associated with longer cycles of PN exposure (eg,≥42 days), and the shorter observation period may mask the preventive effect of SMOF on complications in long-term PN. Meanwhile, the statistical validity of the sample size was insufficient. In this study, there were only 30 samples in each group, and for low-incidence complications such as NEC and ROP, a larger sample size is needed to detect differences between groups. The available sample size may lead to false-negative results due to insufficient statistical power. In addition, the occurrence of complications is regulated by multiple factors. For example, NEC is closely related to the gut

microbiota and feeding mode, and this study did not strictly limit the enteral feeding strategy, which may offset the protective effect of immune improvement, while ROP is affected by oxygen therapy and blood pressure fluctuation, and the individual differences interfere with the between-group comparisons.

PNAC is an adverse reaction that is prone to occur in premature infants after the use of PN, and it has been proposed that the excessive omega-6 fatty acids in soybean fat have a proinflammatory effect and reduce the output of triglycerides, while omega-3 fatty acids tend to exert anti-inflammatory effects and insulin sensitization through the GPR120 receptor.[27] In contrast, Torgalkar et al[28] in a retrospective study of low-birth-weight infants, reported that the incidence of PNAC was not significantly reduced in the SMOF group. In addition, the present study's findings contradict those of the retrospective study by Torgalkar et al in very-low-birth-weight infants, which may stem from differences in populations versus differences in PN protocols. The present study included preterm infants with gestational age<34 weeks, whereas the Torgalkar study population was predominantly of gestational age<28 weeks, and smaller gestational age is accompanied by more immature hepatobiliary metabolic function. The starting dose and escalation strategy of SMOF in this study was more reasonable to avoid lipid overload, whereas higher starting doses in some previous studies may have counteracted the anti-inflammatory effect, suggesting that future studies need to focus on the impact of population characteristics and standardization of PN regimens on complication outcomes. BPD is one of the most common and serious complications of chronic lung disease in premature infants, and lung inflammation is a common outcome of all BPD triggers.[29] There have been several studies with different opinions on the effects of different fat emulsions on the development of BPD in premature infants, and the current studies do not clearly report the effectiveness of SMOF in reducing the risk of BPD. Late-onset sepsis (LOS) in preterm infants is a serious infectious disease. A systemic inflammatory response occurs when pathogens invade the bloodstream of preterm infants and grow, multiply, and produce toxins, which often lack typical clinical manifestations but progress rapidly and severely.[30] NEC is an acquired disease that occurs predominantly in premature infants and is characterized by necrosis of the mucous membranes and even of the deeper layers of the intestine, most often at the end of the ileum.[31] Retinal development is highly dependent on docosahexaenoic acid (DHA) because of its role in regulating capillary integrity, neovascularization, visual function, and inflammation. Premature infants are born with low blood levels of the EFAs DHA and arachidonic acid (ARA), which are associated with the progression of ROP.[32] In the present study, there was no significant difference in the relative incidences of complications between the two groups of premature infants, but the overall incidence of complications in the observation group was lower than that in the control group. Lin et al[33] reported similar findings in a comparative study of the effects of two fat emulsions with different PN durations on the clinical outcomes of premature infants.

Binary logistic regression analyses of the effects of fat emulsion type on the treatment of premature infants revealed significant correlations between fat emulsion type and immune function, complications, and clinical outcomes in premature infants. Compared with MCT/LCT, SMOF is rich in antioxidants such as olive oil, fish oil, and vitamin E. SMOF contains high levels of monounsaturated fatty acids and has a low level of saturated fatty acids, which satisfies the EFA needs of premature infants and, at the same time, is well tolerated, with a rapid energy supply and good clearance of the fat emulsions.[34] Therefore, SMOF has better clinical outcomes for premature infants, effectively improves immunocompetence, reduces the incidence of complications, and improves clinical efficacy. For each unit increase in SMOF, the odds of improvement in immunological indicators increased by a factor of 4.181, the odds of complications increased by a factor of 4.009, and the odds of significant clinical efficacy increased by a factor of 3.671.

We further analyzed the effects of immune indices on clinical outcomes in premature infants and revealed significant correlations between immune proteins (IgA, IgM, and IgG) and immune factors (the percentages of $CD4^+$ T cells, $CD8^+$ T cells, and $CD4^+/CD8^+$ ratio) and clinical outcomes. ROC curve analysis revealed that immune indicators were strongly associated with clinical outcomes ($p < 0.05$), with the AUCs for immune proteins being IgA (0.761), IgG (0.746), and IgM (0.708) and the AUCs for immune factors being $CD4^+$ T cells (0.730), $CD4^+/CD8^+$ (0.677), and $CD8^+$ T cells (0.664). These results indicated that when premature infants were treated with fat emulsions, their immune functions and clinical outcomes were significantly improved, their complication rate was significantly

reduced, and SMOF treatment was more effective, which was further verified by the results of logistic regression analysis of the clinical outcomes, which showed that the treatment effect of SMOF on premature infants was better than that of MCT/LCT. Logistic regression analysis of the immunity indices and clinical outcomes of premature infants revealed that the immunity indices of premature infants were significantly correlated with clinical outcomes, and the ROC curve analysis of the immunity indices was closely correlated with clinical outcomes; therefore, we speculate that the increase in the immunity indices of premature infants may effectively improve clinical outcomes.

This study has some limitations. First, the small sample size (only 60 cases) is insufficient to effectively detect low-incidence complications such as NEC and ROP, which may lead to false-negative results. There are also potential limitations in interpreting nonsignificant results, and the small sample size may lead to insufficient statistical power to detect true differences between groups, which may affect the reliability and extrapolation of the results. Second, there were differences in baseline characteristics (eg, gestational age distribution) of preterm infants in the single-center study, and although there were no significant differences in baseline equilibrium tests, geographic differences in medical practice (eg, timing of enteral feeding initiation, use of breast milk fortification) may have affected the generalizability of the results. Of note, this study did not strictly control for breastfeeding exposure—approximately 15% of preterm infants received more than 50% of their total enteral feedings in breast milk, and components of breast milk, such as IgA and probiotics, may independently influence intestinal immunity, confounding the immunomodulatory effects of fatty emulsions. The study did not measure the dynamic association between breast milk intake and IgA levels, and the confounding effect could not be fully corrected by multivariate analysis. In addition, only short-term PN effects (≤29 days) were observed, and the long-term effects of SMOF versus MCT/LCT on postdischarge growth (eg, neurodevelopmental scores, hepatic and renal function at 6 months of gestational age) could not be assessed in preterm infants. Long-term outcomes, such as PN-associated hepatic injury and immune trajectory, are also critical for clinical decision-making. Future studies need to expand the sample size and conduct multicenter, prospective studies with strict control of feeding practices and incorporation of potential confounders such as genetics and gut microbiota to comprehensively assess the long-term effects of fat emulsions and to further analyze their long-term impact on the growth and development of preterm infants.

In this study, by comparing and analyzing the clinical efficacy of SMOF and MCT/LCT in preterm PN, the immune indicators of premature infants in the observation group with PN durations of 15–21 days, 22–28 days, and ≥29 days were greater than those in the control group ($p < 0.05$). The clinical efficacy of the observation group was greater than that of the control group, with the total rate of complications lower than that of the control group ($p < 0.05$). The logistic regression analysis indicated that fat emulsion type was associated with the immune indicators, complications, and clinical outcomes of premature infants and that the immune indicators of premature infants were associated with the clinical outcomes ($p < 0.05$). The ROC curve analysis indicated that immune indicators were strongly associated with clinical outcomes ($p < 0.05$). These results suggest that both interventions enhance immunity in preterm infants and that SMOF may be more effective than MCT/LCT, while there is a correlation between improved immune function in preterm infants and optimized clinical outcomes. This finding provides an initial reference direction for the selection of clinical nutritional support programs. This study has limitations such as small sample size, single-center design, and short observation period, and potential confounders such as gut microbiota and genetic polymorphisms were not fully included, while preterm infants receiving breastfeeding may interfere with immune indicators. In view of this, these findings only suggest that SMOF may have potential advantages in PN for preterm infants, but its wide clinical application still needs to be further validated by multicenter studies with larger sample sizes, as well as strict control of feeding methods, longer observation periods, and improved monitoring of immune markers to adequately assess the long-term safety and efficacy of SMOF.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of the Dongxihu District People's Hospital. Signed informed consent was obtained from a legal guardian for each participant.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

The data supporting the results of this study are not publicly available at this time due to privacy protections for preterm infants and related ethical constraints.

AI ASSISTANCE DISCLOSURE

No artificial intelligence (AI) tools were used in the preparation of this manuscript.

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