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SYSTEMATIC REVIEW

Impact of SMOFlipid on Clinical Outcomes in Neonates Receiving Parenteral Nutrition: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Tao He[1], Jianqiong Huang[1], Danwei Ren[1], Sen Yang[1,2,*]

[1]Department of Pediatrics, Chengdu Fifth People's Hospital, Chengdu, Sichuan, China
[2]School of Medical and Life Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China
*Correspondence: 18702825303@163.com (Sen Yang)

Abstract

Aims/Background Neonatal morbidity, including various diseases such as sepsis, cholestasis, and bronchopulmonary dysplasia (BPD), is a significant concern, especially in preterm infants. Selecting the appropriate lipid emulsion in parenteral nutrition (PN) is essential to improve clinical outcomes. This analysis aimed to assess the impact of a novel composite lipid emulsion, SMOFlipid, on neonates receiving PN.

Methods A systematic review and meta-analysis of randomized controlled trials (RCTs) were conducted. We compared SMOFlipid to various other lipid emulsions in PN received by infants. Research findings that addressed outcomes such as mortality, sepsis, cholestasis, necrotizing enterocolitis (NEC), BPD, patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), and length of hospital stay were included. Subgroup analyses were conducted based on gestational age (GA). Twenty RCTs involving 1904 neonates were included.

Results Compared to other lipid emulsions, SMOFlipid significantly reduced the cholestasis risk (risk ratio (RR): 0.65, 95% confidence interval (CI): 0.48–0.87, $p = 0.004$, $I^2 = 0\%$). However, the incidence related to IVH, BPD, ROP, NEC, and PDA (excluding an infant subgroup with GA <28 weeks), mortality, sepsis, and duration of hospital stay did not exhibit any substantial variations. The subgroup analysis indicated a decline in PDA incidence (RR: 0.88, 95% CI: 0.79–0.99, $p = 0.04$, $I^2 = 0\%$) among extremely premature infants receiving SMOFlipid.

Conclusion SMOFlipid offers a promising option for neonatal PN, particularly for reducing cholestasis in preterm infants and PDA in extremely premature infants. Further investigations into its comprehensive benefits and long-term effects are warranted.

Key words: SMOFlipid; lipid emulsion; parenteral nutrition; neonatal morbidity; systematic review; meta-analysis

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Introduction

Neonatal morbidity is a serious public health issue, particularly for premature infants who are more susceptible to adverse outcomes (De Costa et al, 2021). A number of neonatal complications require addressing under this context since these diseases could lead to unpleasant consequences of varying severity, including long-term effects on cognitive, motor, and behavioural development (Bell et al, 2022; van Dokkum et al, 2021).

Parenteral nutrition (PN) is a crucial component of neonatal care and treatment, particularly for infants who face difficulties with enteral feeding or require additional nutrients for optimal growth and development (Moltu et al, 2021). One key aspect of PN is the use of lipid emulsions, which provide the energy and crucial fatty acids needed by cells for their proper functioning, along with facilitating growth processes (Tota et al, 2022). Nonetheless, conventional lipid emulsions present a challenge due to higher levels of ω-6 polyunsaturated fatty acids (PUFA) content compared to lower levels of ω-3 PUFA. These emulsions are potentially conducive to controlling lipid peroxidation, oxidative stress, as well as inflammatory responses, which are potential factors of neonatal complications (Li et al, 2023; Djuricic and Calder, 2021).

With an ideal ω-6:ω-3 ratio, soybean oil-medium chain triglyceride-olive oil-fish oil (SMOF) has been gradually applied as a unique complex lipid emulsion in recent years (Goulet, 2024). Moreover, SMOFlipid substantially boosts levels of vitamin E and α-tocopherol, which can mitigate oxidative stress and inflammation (Li et al, 2023; Xu et al, 2021). From a theoretical perspective, the unique composition of SMOFlipid confers superior clinical efficacy on newborns compared to traditional lipid emulsions. Earlier research indicated that newborns receiving SMOFlipid, as compared to those taking other types of lipid emulsions, demonstrated improved biochemical markers, such as lower triglycerides, reduced inflammation, and better liver function (Greenberg et al, 2023; Papandreou et al, 2020b; Rumore et al, 2021). Nevertheless, the impact of SMOFlipid on clinically relevant neonatal morbidities remains unclear.

A few previous meta-analyses of randomized controlled trials (RCTs) evaluated the impacts of lipid emulsions containing fish oil (FO) on neonatal patients (Kapoor et al, 2019; Vayalthrikkovil et al, 2017; Zou et al, 2022). However, these studies lacked a dedicated focus on SMOFlipid and did not encompass all the outcomes of interest. In light of several recently published RCTs (Costa et al, 2021; Yang et al, 2023), we recognized the need to incorporate these studies into a new meta-analysis since they were not included in the previous meta-analyses supporting the efficacy of SMOFlipid's in neonatal patients. Therefore, we aimed to conduct a systematic meta-analysis of RCTs on this topic to more comprehensively evaluate the effect of SMOFlipid emulsions on the clinical outcomes of neonatal patients receiving PN.

Methods

Literature Search and Search Strategy

This meta-analysis was conducted in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (**Supplementary Table 1**) (Page et al, 2021). The registration number is CRD42019127666. We searched the Embase, PubMed, as well as Cochrane Library databases thoroughly for all references that met the inclusion criteria, spanning up to January 1, 2024. The search keywords included "SMOF", "soybean oil-medium chain triglycerides-olive oil-fish oil lipid emulsion (SMOF-LE)", "SMOFlipid", "fish

oil, medium-chain triglycerides, olive oil and soya oil (FMOS)", "FMOS lipid", "medium-chain triglycerides, olive oil, soybean oil, and fish oil (MOSF)", "composite lipid emulsion", "multi-oil fat emulsion", "preterm", "premature infant", "low birth weight infant", "newborn", "neonatal", and "neonate". Literature search was conducted by two independent reviewers in order to prevent potential omissions. Only articles that are available in full text were selected. Additionally, to search for further research that might not have been found in the database search, we manually screened the reference lists from the retrieved articles and pertinent systematic reviews.

Study Selection

To identify eligible research, two reviewers independently examined the titles and abstracts of each study. The full-text articles of all potentially pertinent studies were retrieved and reviewed by two evaluators individually to determine each study's eligibility in accordance with the inclusion criteria. In case of disagreement between the two evaluators, a third reviewer would be consulted to reach a consensus.

Inclusion and Exclusion Criteria

RCTs that met the following criteria were included: (1) Participants: Infants who received PN. (2) Intervention: SMOFlipid as the main lipid emulsion's utilization. (3) Comparison: Application of additional lipid emulsions pertaining to PN. (4) Outcomes: Consideration of at least one of the neonatal clinical outcome parameters like the incidence of cholestasis, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), mortality, patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), sepsis, as well as the length of hospital stay. Studies were excluded if they met any of the following criteria: (1) non-randomized trials, (2) studies involving animals or *in vitro* experiments, (3) studies not reporting on at least one of the predefined neonatal clinical outcomes, (4) duplicate publications, and (5) articles not available in full text or published in languages other than English without available translations.

Data Extraction

Two reviewers retrieved data from the included research with the help of a standard data extraction form. Information such as the first author's name, publication year of the study, study region, sample size, infants' gestational age (GA), lipid emulsions used in the experimental and control groups, length of PN administration, as well as neonatal clinical outcomes were obtained from every research.

Risk of Bias Assessment

Using the Revised Cochrane Risk of Bias Tool RoB 2.0 (version August 2019, The Cochrane Collaboration, London, UK), two reviewers assessed the included RCTs' RoB on their own (Sterne et al, 2019). The following categories were assessed by RoB 2.0 for each trial that satisfies eligibility requirements: outcome measurement, reported results, deviations from planned interventions, randomization process, as well as missing outcome data. There were three classifications for

the potential RoB judgments: high risk, some concerns, as well as low risk. Using the highest risk assigned to any specific domain, we calculated the overall RoB for each trial. Any differences that might have surfaced were addressed by discussing with or consulting a third reviewer.

Statistical Analysis

For the meta-analysis, Review Manager software (RevMan 5.4.1, The Cochrane Collaboration, London, UK) was utilized. Pertaining to dichotomous outcomes, the effect sizes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). The mean differences (MDs) with 95% CIs for continuous outcomes were calculated. For dichotomous variables exhibiting zero-event occurrences, we applied Laplace smoothing for correction (Ju et al, 2020). A random-effects model was used to determine the overall effect size. The I^2 statistic was utilized to evaluate the degree of heterogeneity among the studies, with values $>50\%$ indicating significant heterogeneity. The effect of SMOFlipid may vary based on the GA, and to clarify these differences, a subgroup analysis was performed with different mean GA (<28 weeks and ≥ 28 weeks) and mean PN days (<14 days and ≥ 14 days). We conducted a sensitivity analysis by sequentially removing and reanalyzing data from each individual study to assess the robustness of the findings. Publication bias was quantitatively assessed using Egger's regression test, where a p-value < 0.10 indicates significant publication bias.

Results

Study Selection

A thorough search of the literature turned up 328 records, of which 29 were duplicates. Afterwards, 87 full-text articles were evaluated for eligibility soon after the titles and abstracts of the remaining 212 articles were screened. Ultimately, this systematic review and meta-analysis included 20 RCTs that met the predetermined inclusion criteria. The flowchart of the particular study selection procedure is shown in Fig. 1.

Included Studies and Their Characteristics

The 20 included RCTs (Ariyawangso et al, 2014; Beken et al, 2014; Costa et al, 2021; D'Ascenzo et al, 2014; Deshpande et al, 2014; Diamond et al, 2017; Hsiao et al, 2019; Jiang et al, 2019; Najm et al, 2017; Ozkan et al, 2019; Papandreou et al, 2020a; Repa et al, 2018; Savini et al, 2013; Skouroliakou et al, 2010, 2016; Techasatid et al, 2017; Uthaya et al, 2016; Vlaardingerbroek et al, 2014; Yang et al, 2023; Yildizdas et al, 2019) involved a total of 1904 neonates, among which 945 were administered SMOFlipid and 959 were administered other lipid emulsions in PN. Table 1 provides a summary of the features of the 20 studies that were included. These above-mentioned studies were published from 2010 to 2023. One of the included studies did not report the GA of the newborns (Jiang et al, 2019), and the median GA of the infants in the additional research varied between 25.5 weeks and 34.5 weeks. The number of PN days of the participants varied from 7 to 59.5. The lipid emulsion used in all experimental groups was SMOFlipid® (Fresenius Kabi,

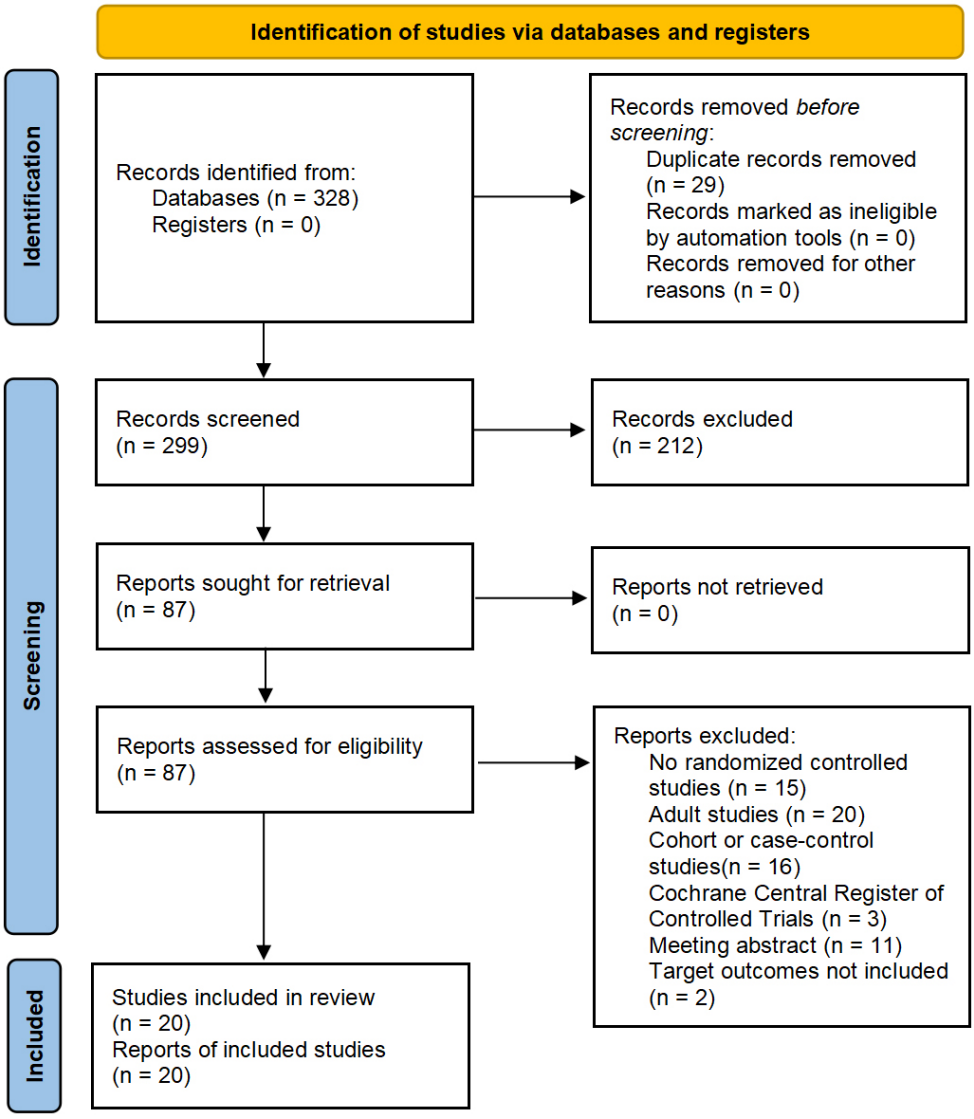

Fig. 1. Flow chart depicting the process of literature screening.

Bad Homburg, Germany). In contrast, there were several types of lipid emulsions used in the control group, eleven of which were Intralipid® [Fresenius Kabi, Bad Homburg, Germany, 100% soybean oil (SO)] (Ariyawangso et al, 2014; Beken et al, 2014; Costa et al, 2021; D'Ascenzo et al, 2014; Diamond et al, 2017; Papandreou et al, 2020a; Repa et al, 2018; Skouroliakou et al, 2010, 2016; Uthaya et al, 2016; Vlaardingerbroek et al, 2014), one was expressed as pure SO (Techasatid et al, 2017), four were ClinOleic® [Baxter Healthcare Corporation, Deerfield, IL, USA, comprising 80% olive oil (OO) and 20% SO] (Deshpande et al, 2014; Najm et al, 2017; Ozkan et al, 2019; Yildizdas et al, 2019), in addition to the lipid emulsions used in another three groups all consisting of 50% medium-chain triglycerides (MCT) as well as 50% SO, which includes Lipofudin® (B. Braun Melsungen AG, Melsungen, Germany), Lipovenoes® (Fresenius Kabi, Bad Homburg, Germany),

Table 1. Clinical data of the randomized clinical trials included in the meta-analysis.

Study	Region	Participants (P/C)	GA (wk; P/C), mean ± SD or median (range)	Intervention (P/C)	PN duration (d; P/C), mean ± SD or median (range)	Outcome
(Skouroliakou et al, 2010)	Greece	14/18	28.21 ± 2.89/30.39 ± 1.58	SMOFlipid®/Intralipid®	41.00 ± 22.97/28.82 ± 13.93	⑨
(Savini et al, 2013)	Italy	28/116	27.5 ± 2.0/28.2 ± 2.1	SMOFlipid®/Intralipid® +Lipofundin®+Lipidem® +ClinOleic®	19.0 ± 4.3/21.6 ± 5.6, 21.7 ± 6.9, 20.9 ± 5.5, 21.6 ± 6.5	①②③⑥⑧
(Ariyawangso et al, 2014)	Thailand	21/21	33.3 ± 4.5/32.9 ± 4.2	SMOFlipid®/Intralipid®	22.48 ± 8.46/20.86 ± 5.50	③⑧
(Beken et al, 2014)	Turkey	40/40	30 (28–31)/30 (27–31)	SMOFlipid®/Intralipid®	14 (10–28)/14 (10–21)	①②③④⑤⑦⑧
(Deshpande et al, 2014)	Australia	17/17	26.73 ± 1.62/26.45 ± 1.92	SMOFlipid®/Clinoleic®	7/7	②④⑥⑦
(D'Ascenzo et al, 2014)	Italy	39/41	28.1 ± 2.0/28.2 ± 2.0	SMOFlipid®/Intralipid®	18/18	①②③④⑤⑥⑦⑧
(Vlaardingerbroek et al, 2014)	Netherlands	48/48	27.1 ± 2.3/27.2 ± 1.9	SMOFlipid®/Intralipid®	11 (9–14)/12 (9–16)	①②③④⑤⑥⑦⑧⑨
(Skouroliakou et al, 2016)	Greece	25/26	29.2 ± 1.6/29.1 ± 1.3	SMOFlipid®/Intralipid®	>15/>15	①②⑧
(Diamond et al, 2017)	Canada	11/13	34.5 (32.4–36.7)/35.2 (33.2–37.1)	SMOFlipid®/Intralipid®	59.5 (38.5–73.5)/56 (39.9–74.9)	③⑧
(Uthaya et al, 2016)	England	85/83	27.5 ± 2.4/27.8 ± 1.9	SMOFlipid®/Intralipid®	12 (9–16)/12 (9–18)	①④⑧
(Najm et al, 2017)	Sweden	41/37	25.5 ± 1.3/25.6 ± 1.6	SMOFlipid®/Clinoleic®	12 (2–72)/12 (2–92)	①②③⑤⑥⑧
(Repa et al, 2018)	Austria	110/113	25.9 (24.9–27.4)/26.3 (25.0–28.0)	SMOFlipid®/Intralipid®	23 (17–37)/24 (17–35)	①②③④⑤⑥⑦⑧
(Techasatid et al, 2017)	Bangkok	22/22	27.6 ± 2.2/28.4 ± 1.2	SMOF®/pure soybean oil	11.9 ± 8.1/9.9 ± 5.9	②③③④⑤⑥⑦⑧⑨
(Jiang et al, 2019)	China	22/24	-/-	SMOFlipid®/MCT/LCT	28/28	③
(Hsiao et al, 2019)	Taiwan of China	30/30	28.5 ± 2.9/28.3 ± 2.9	SMOFlipid®/Lipovenoes®	32.59 ± 16.84/31.62 ± 17.56	①②③④⑤⑦⑧⑨

Table 1. Continued.

Study	Region	Participants (P/C)	GA (wk; P/C), mean ± SD or median (range)	Intervention (P/C)	PN duration (d; P/C), mean ± SD or median (range)	Outcome
(Yildizdas et al, 2019)	Turkey	34/33	29.2 ± 2.3/29.3 ± 2.6	SMOFlipid®/Clinoleic®	20.8 ± 13.7/22.1 ± 14.1	①②③④⑤⑥⑦⑨
(Ozkan et al, 2019)	Turkey	42/47	28.1 ± 1.2/28 ± 1.1	SMOFlipid®/Clinoleic®	14/14	①②③⑤⑥⑦⑧
(Papandreou et al, 2020a)	Greece	31/35	29.2 ± 1.9/29.3 ± 1.7	SMOFlipid®/Intralipid®	16.7 ± 2.0/17.3 ± 1.4	②⑤⑥⑦⑧⑨
(Costa et al, 2021)	Italy	51/50	27.8 ± 2.15/27.7 ± 2.1	SMOFlipid®/Intralipid®	39.7 ± 31.4/33.4 ± 28.4	①②③④⑤⑥⑦⑧⑨
(Yang et al, 2023)	China	234/231	29.9 (28.5–31.1)/30.1 (28.9–31.4)	SMOFlipid®/Lipofundin®	26.0 (20.0–35.3)/25.0 (18.0–34.0)	①②③④⑤⑥⑦⑧⑨

Notes: ① Incidence of cholestasis; ② Incidence of bronchopulmonary dysplasia; ③ Incidence of necrotizing enterocolitis; ④ Mortality; ⑤ Incidence of retinopathy of prematurity; ⑥ Incidence of patent ductus arteriosus; ⑦ Incidence of intraventricular hemorrhage; ⑧ Incidence of sepsis; ⑨ Days of hospital stay.
Abbreviations: GA, gestational age; P/C, experimental/control; PN, parenteral nutrition; SD, standard deviation; MCT, medium-chain triglycerides; LCT, long-chain triglycerides; SMOF, soybean oil-medium chain triglyceride-olive oil-fish oil.
SMOF® Fresenius Kabi, containing 30% soybean oil, 30% MCT, 25% olive oil, 15% fish oil; Intralipid® Fresenius Kabi, containing 100% soybean oil; Lipofudin® B. Braun, containing 50% MCT and 50% soybean oil; Lipidem® B. Braun, containing 50% MCT, 40% soybean oil, and 10% fish oil; ClinOleic® Baxter spa, containing 80% olive oil and 20% soybean oil; Lipovenoes® Fresenius Kabi, containing 50% MCT and 50% soybean oil.

and MCT/long-chain triglycerides (LCT) (Baxter Qiaoguang, Healthcare Co, Ltd., Guangzhou, China) (Hsiao et al, 2019; Jiang et al, 2019; Yang et al, 2023). Moreover, there was another study with control groups that contained four lipid emulsions, including Lipofudin® in addition to Lipidem® (B. Braun Melsungen AG, Melsungen, Germany) in addition to Intralipid® and ClinOleic® (Savini et al, 2013). Finally, the number of clinical outcomes considered in each included study varied, ranging from one to nine.

Risk of Bias Assessment

Since there were deviations from planned interventions brought about by the medical team's lack of blinding in this investigation, we found that one RCT has a high RoB. The remaining trials were rated as having some concern or a low RoB. Fig. 2 presents a thorough overview pertaining to each study's RoB assessment.

Clinical Outcomes

For each of these outcomes including PDA, cholestasis, ROP, NEC, and IVH, we corrected the data from studies with zero-event occurrences using Laplace smoothing, respectively. Figs. 3,4,5,6,7,8,9,10,11 depict the impact of SMOFlipid on the clinical outcomes. Our meta-analysis of RCTs revealed that neonates administered with SMOFlipid exhibited a significantly reduced risk of cholestasis (RR: 0.65, 95% CI: 0.48–0.87, $p = 0.004$, $I^2 = 0\%$) (Fig. 3). Contrastingly, we discovered no significant differences in the risks for BPD contributed by SMOFlipid and other lipid emulsions (RR: 0.99, 95% CI: 0.86–1.15, $p = 0.92$, $I^2 = 12\%$) (Fig. 4), NEC (RR: 1.20, 95% CI: 0.88–1.62, $p = 0.25$, $I^2 = 0\%$) (Fig. 5), mortality (RR: 1.10, 95% CI: 0.75–1.62, $p = 0.62$, $I^2 = 0\%$) (Fig. 6), ROP (RR: 0.93, 95% CI: 0.78–1.10, $p = 0.40$, $I^2 = 0\%$) (Fig. 7), PDA (RR: 0.96, 95% CI: 0.87–1.06, $p = 0.41$, $I^2 = 0\%$) (Fig. 8), IVH (RR: 0.96, 95% CI: 0.76–1.21, $p = 0.73$, $I^2 = 0\%$) (Fig. 9), and sepsis (RR: 1.05, 95% CI: 0.86–1.27, $p = 0.66$, $I^2 = 0\%$) (Fig. 10). Furthermore, no substantial difference could be found when it comes to the length of hospital stay (MD: 1.77, 95% CI: 1.94–5.48, $p = 0.35$, $I^2 = 39\%$) (Fig. 11) between these two groups.

Subgroup Analyses

The outcomes generated by the subgroup analysis are shown in Table 2. For our examination, we divided the studies into subgroups based on the mean GA. Notably, in Yang et al (2023)'s study, neonates were classified into two cohorts: those with a GA $\geq$28 weeks and those with a GA $<$28 weeks, and we analyzed the data from these two cohorts in the two subgroups, respectively. The subgroup analysis of studies involving infants with GA less than 28 weeks demonstrated a significant decrease in cholestasis and PDA incidence when using SMOFlipid in contrast to the control group. Similarly, the subgroup analysis of studies with infants receiving PN for over 14 days showed a noticeable decrease in the cholestasis incidence when SMOFlipid was used compared to the control group. However, subgroup analyses for the remaining outcomes did not reveal substantial differences between the two groups.

Fig. 2. Risk of bias assessment of included studies using Risk of Bias Tool RoB 2.0 (version August 2019, The Cochrane Collaboration, London, UK).

Sensitivity Analysis

Sensitivity analyses for each outcome were performed by removing each included study individually. As presented in Table 2, we reported the minimum and maximum point estimates derived following the removal of each study, and none of the pooled estimates for any of the outcomes changed significantly.

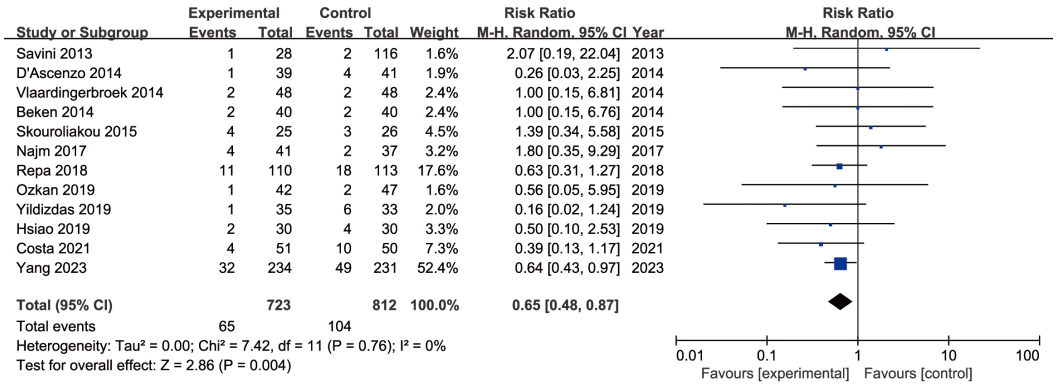

Fig. 3. Forest plot for the incidence of cholestasis. CI, confidence interval.

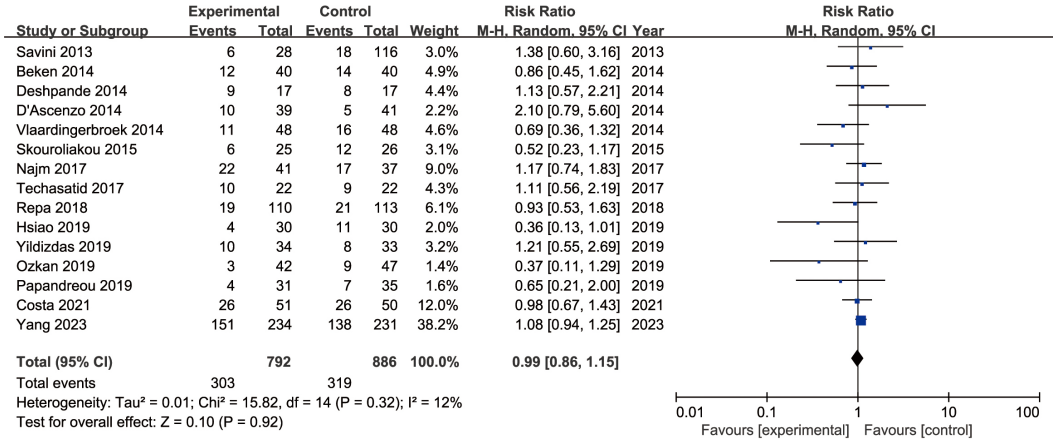

Fig. 4. Forest plot for the incidence of bronchopulmonary dysplasia.

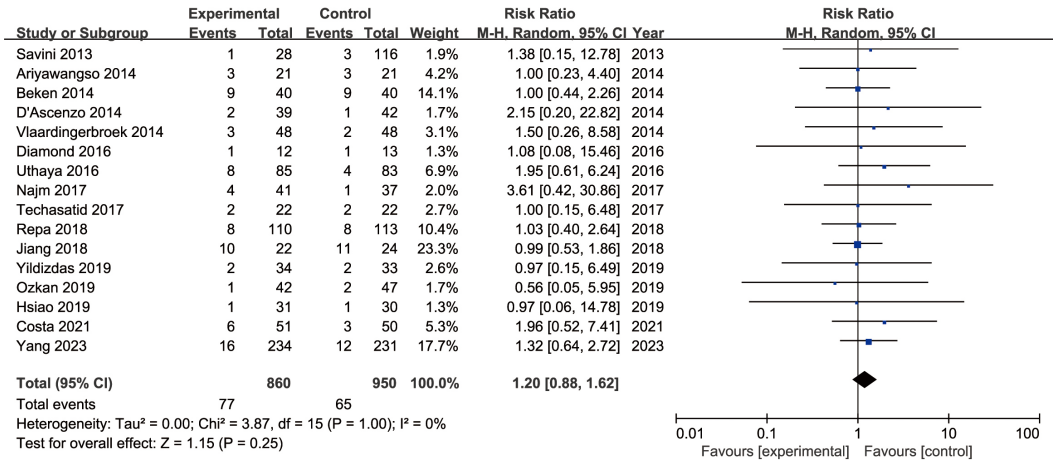

Fig. 5. Forest plot for the incidence of necrotizing enterocolitis.

Publication Bias

The findings of Egger's test, which was used to determine the presence of publication bias, are outlined in Table 2 (refer to **Supplementary Figs. 1–9** for details). Interestingly, the Egger's regression test revealed that there was no substantial pub-

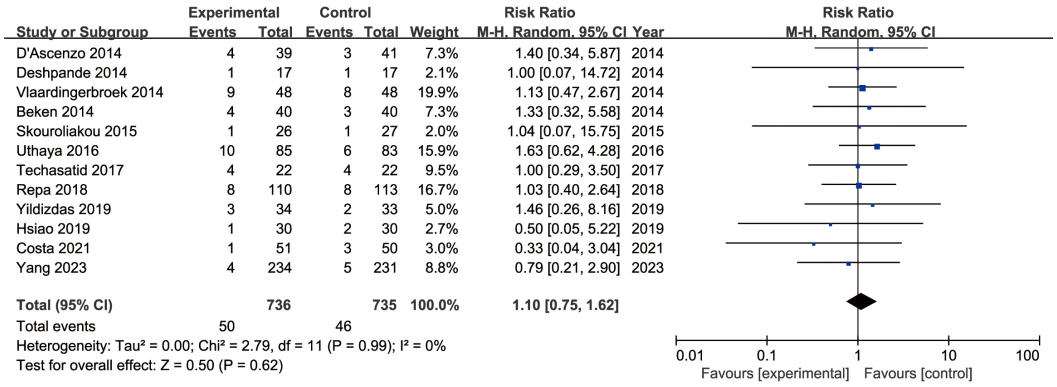

Fig. 6. Forest plot for the incidence of mortality.

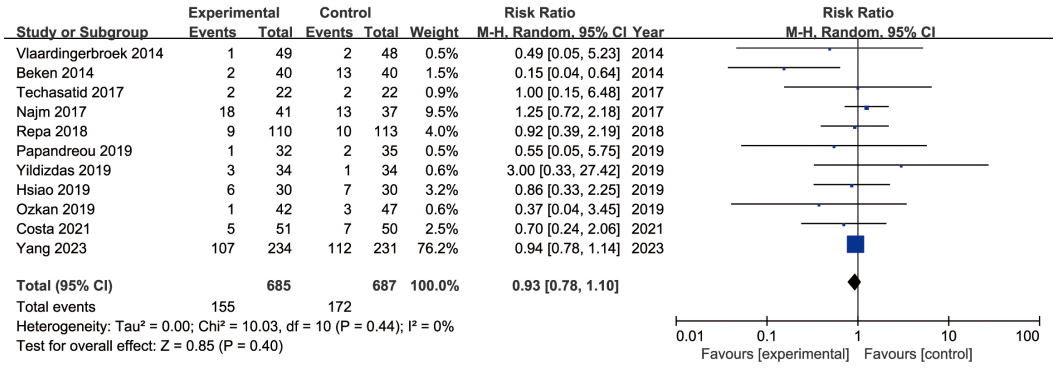

Fig. 7. Forest plot for the incidence of retinopathy of prematurity.

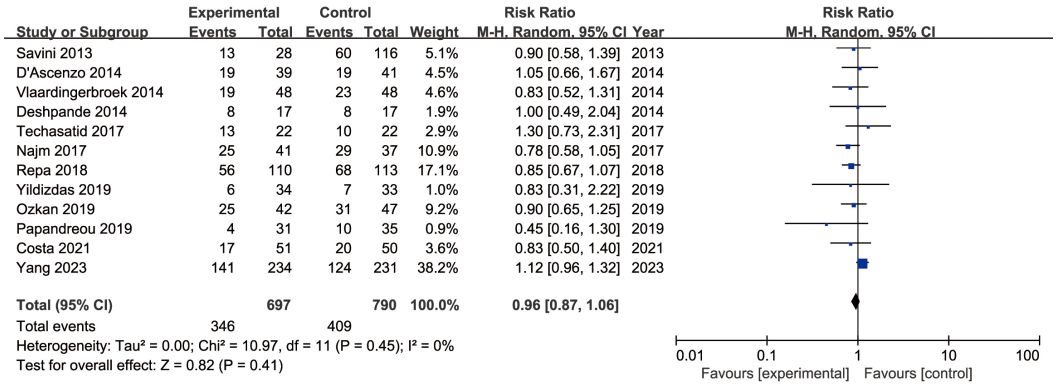

Fig. 8. Forest plot for incidence of the patent ductus arteriosus.

lication bias for neonatal clinical outcomes, with a *p*-value exceeding 0.10 for all outcomes.

Discussion

In this systematic review tied with a meta-analysis of 20 RCTs involving 1904 neonates, we discovered that SMOFlipid, a novel composite lipid emulsion that combines the benefits of various oils, exhibits a significant beneficial impact in decreasing the cholestasis incidence among neonates receiving PN, when compared

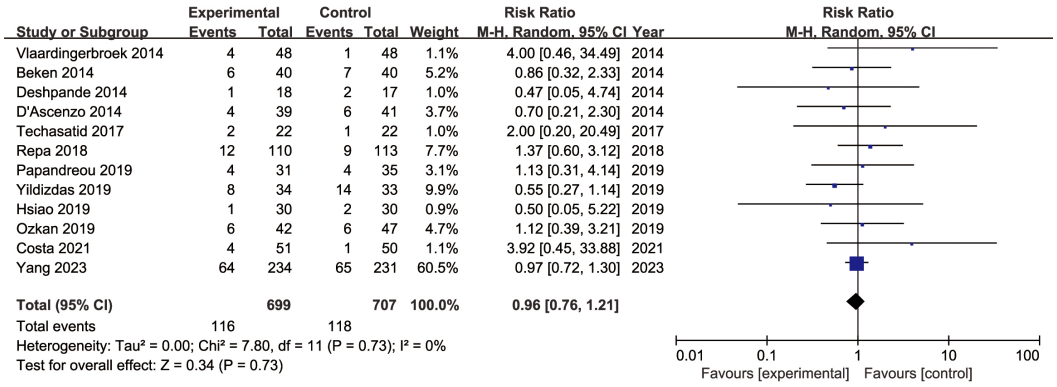

Fig. 9. Forest plot for the incidence of intraventricular hemorrhage.

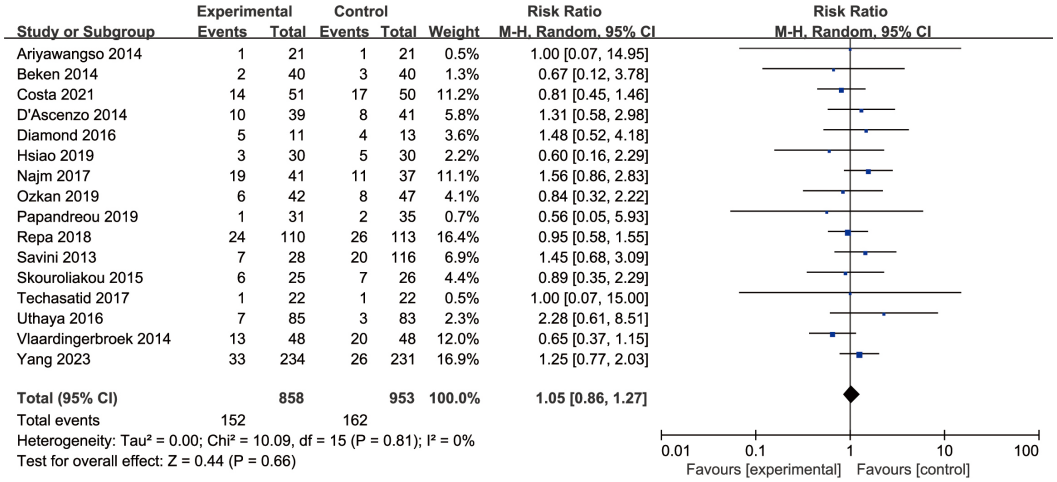

Fig. 10. Forest plot for the incidence of sepsis.

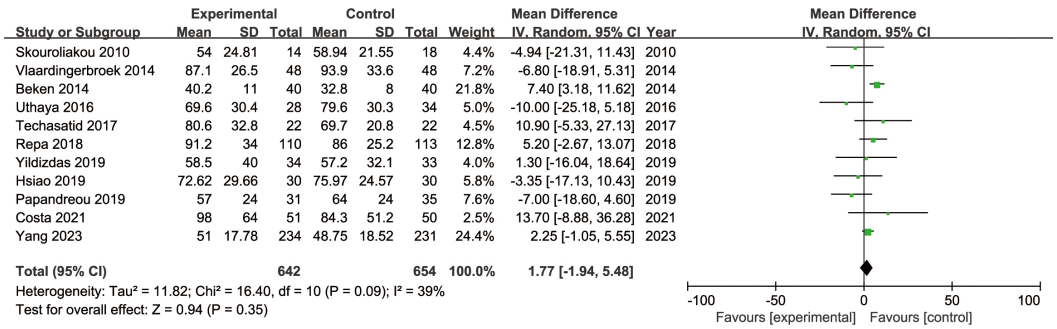

Fig. 11. Forest plot for the length of hospital stay.

with other lipid emulsions. Furthermore, our subgroup analysis indicated that SMOF lipid also significantly lowers the risk of PDA in extremely premature infants (GA <28 weeks).

Our study aligns with prior research (Zou et al, 2022), suggesting that SMOFlipid can significantly reduce the cholestasis risk among infants receiving PN. This positive outcome can likely be attributed to a balanced ratio of ω-6 to ω-3 PUFAs, derived from SO, MCT, OO and FO. This composition helps mitigate oxidative

Table 2. The results of subgroup analysis, sensitivity analysis and publication bias.

Comparison group	RR	95% CI	I^2	*p*-value	N	RPE	PB
Cholestasis						0.63–0.68	0.799
Median GA <28 wk	0.59	0.40–0.87	0%	0.01	9		
Median GA ≥28 wk	0.72	0.45–1.17	3%	0.19	4		
Median PN <14 d	0.72	0.45–1.17	3%	0.19	4		
Median PN ≥14 d	0.62	0.45–0.84	0%	0.01	8		
ROP						0.88–0.95	0.322
Median GA <28 wk	1.07	0.90–1.29	0%	0.44	9		
Median GA ≥28 wk	0.64	0.22–1.87	59%	0.41	4		
Median PN <14 d	0.57	0.21–1.58	56%	0.28	5		
Median PN ≥14 d	0.94	0.78–1.12	0%	0.47	7		
PDA						0.87–0.99	0.150
Median GA <28 wk	0.88	0.79–0.99	0%	0.04	10		
Median GA ≥28 wk	0.92	0.54–1.58	46%	0.76	3		
Median PN <14 d	0.88	0.73–1.05	0%	0.16	5		
Median PN ≥14 d	0.97	0.83–1.20	16%	0.66	7		
BPD						0.94–1.04	0.122
Median GA <28 wk	1.01	0.85–1.20	20%	0.90	11		
Median GA ≥28 wk	1.00	0.82–1.23	7%	0.98	5		
Median PN <14 d	0.96	0.74–1.24	0%	0.74	9		
Median PN ≥14 d	0.99	0.80–1.22	26%	0.91	6		
NEC						1.19–1.34	0.749
Median GA <28 wk	1.18	0.80–1.73	0%	0.40	12		
Median GA ≥28 wk	1.23	0.73–2.10	0%	0.44	5		
Median PN <14 d	1.28	0.73–2.23	0%	0.38	6		
Median PN ≥14 d	1.16	0.81–1.67	0%	0.43	10		
IVH						0.93–1.02	0.517
Median GA <28 wk	0.94	0.63–1.41	0%	0.78	9		
Median GA ≥28 wk	0.97	0.73–1.28	0%	0.82	4		
Median PN <14 d	1.10	0.58–2.07	0%	0.77	5		
Median PN ≥14 d	0.94	0.74–1.20	0%	0.63	7		
Sepsis						0.99–1.11	0.852
Median GA <28 wk	0.99	0.79–1.25	0%	0.95	11		
Median GA ≥28 wk	1.23	0.82–1.83	0%	0.33	6		
Median PN <14 d	1.02	0.67–1.57	18%	0.91	6		
Median PN ≥14 d	1.06	0.84–1.35	0%	0.63	10		
Death						1.02–1.15	0.132
Median GA <28 wk	1.31	0.51–3.42	0%	0.65	5		
Median GA ≥28 wk	1.11	0.71–1.72	0%	0.58	9		
Median PN <14 d	1.25	0.74–2.11	0%	0.40	5		
Median PN ≥14 d	0.96	0.55–1.68	0%	0.88	8		
Length of hospital stay*	MD					0.61–2.67	0.259
Median GA <28 wk	0.14	–5.90–6.18	27%	0.96	8		

Table 2. Continued.

Comparison group	RR	95% CI	I^2	*p*-value	N	RPE	PB
Median GA ≥28 wk	1.71	–8.22–11.64	63%	0.74	4		
Median PN <14 d	1.09	–8.63–10.81	67%	0.83	4		
Median PN ≥14 d	1.80	–0.98–4.58	0%	0.20	7		

Note: * This outcome was characterized by the mean difference as the effect size.

Abbreviations: N, Number of studies; RR, risk ratio; CI, confidence interval; RPE, Re-synthesized point estimates; PB, publication bias; GA, gestational age; PN, parenteral nutrition; ROP, retinopathy of prematurity; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage.

stress and inflammation, which are implicated in the pathogenesis of cholestasis. Specifically, the high content of ω-3 PUFAs in SMOFlipid promotes the production of anti-inflammatory mediators and modulates the expression of genes related to bile acid synthesis and transport, thus reducing bile acid cytotoxicity (Bechynska et al, 2019; Fuchs and Trauner, 2022; Harwood, 2023; Leguina-Ruzzi and Ortiz, 2018). Moreover, the olive oil component, rich in oleic acid, enhances bile solubility and prevents bile stasis by increasing phospholipid levels in bile (Lu et al, 2024). Lastly, SMOFlipid boasts a high level of α-tocopherol, a potent antioxidant that further protects hepatocytes from oxidative damage (Forman and Zhang, 2021).

Regarding PDA, the subgroup analysis for infants with GA <28 weeks demonstrated a significant reduction in PDA incidence following the utilization of SMOFlipid. This finding can be explained by several attributing factors. First, extremely premature infants have a higher incidence and severity of PDA and may benefit more from the anti-inflammatory and vasodilatory properties of SMOFlipid (Hamrick et al, 2020). Second, the ω-3 PUFAs in SMOFlipid help modulate inflammatory responses and promote the production of nitric oxide, a vasodilator essential for ductal closure (Al-Turkait et al, 2022; Spector and Kim, 2019). Additionally, the antioxidant properties of SMOFlipid may protect the ductal tissue from oxidative stress, which is exacerbated by oxygen therapy and mechanical ventilation commonly required in extremely premature infants (Forsberg et al, 2021).

Compared to Vayalthrikkovil et al (2017)'s study, which presented the prevention of severe ROP by FO-based lipid emulsions, our study established that SMOFlipid possesses an insignificant impact on the all-stage ROP incidence, as well as the other neonatal clinical outcomes, which could be attributed to multiple factors. Firstly, certain outcomes like BPD, NEC, ROP, and IVH are influenced by a complex interplay of factors beyond lipid emulsions, including maternal chorioamnionitis, premature rupture of membranes, birth weight, oxygen therapy, infection, feeding intolerance, and the duration of mechanical ventilation (Cai et al, 2021; Iijima, 2023; Wu et al, 2021). Secondly, given the rarity of outcomes such as mortality and sepsis, larger cohorts and extended follow-up duration are required

to unveil significant distinctions in these aspects between groups taking different types of lipid emulsions. Furthermore, variables like the length of hospital stay are shaped by the clinical protocols and discharge standards of different institutions, which may not accurately mirror the actual effectiveness of lipid emulsions.

This meta-analysis demonstrates multiple strengths. Firstly, the studies incorporated in our research were culled from 20 studies originating from a diverse set of countries and having a wide geographical representation. This diversity bolsters the applicability of our findings to a broader context. Second, sensitivity analyses determined that no single study significantly influenced all the outcomes of our study. Furthermore, Egger's tests revealed no indication of publication bias for any of the outcomes, indicating the robustness and stability of our findings.

Despite the valuable insights, this meta-analysis has a few noteworthy limitations. Firstly, the majority of the research we incorporated featured a small sample size. To enhance the reliability of any meta-analysis, it is crucial to conduct large-scale, multicenter studies. Second, we limited the scope of our literature search only to English databases. Studies published in languages other than English might have gone unnoticed. Third, we only explored the effects of GA and PN on the efficacy of SMOFlipid. However, other influential factors that have not yet been explored need to be investigated in further research. Fourth, we corrected the partial data using the Laplace smoothing method, which inevitably introduced potential bias. In addition, the studies we included only addressed individual comparisons between SMOFlipid and other conventional lipid emulsions, limiting the possibility of conducting a network meta-analysis to systematically compare the degree of superiority or inferiority among all types of lipid emulsions. Lastly, the outcomes we analyzed represent short-term results post-SMOFlipid intervention, leaving long-term consequences of SMOFlipid intervention, especially those on neurodevelopment, largely unexplored.

Conclusion

In conclusion, this systematic review, along with the meta-analysis of 20 RCTs, provides evidence that SMOFlipid represents a promising option for PN in neonates, especially for reducing cholestasis in preterm infants and PDA in extremely premature infants. However, the available data is not sufficient to assess if SMOF is beneficial in lowering ROP, NEC, IVH, BPD, mortality and sepsis, as well as shortening the length of hospital stay. Additionally, superior RCTs with larger sample sizes and extended follow-up duration are required to substantiate these findings, explore long-term outcomes, and understand the full spectrum of benefits and limitations associated with SMOFlipid use in neonatal patients.

Key Points

- Neonatal morbidity in neonates, especially in preterm infants, is a major concern.
- This study assessed how a novel composite lipid emulsion identified as SMOFlipid affected newborns receiving parenteral nutrition (PN).
- Twenty randomized controlled trials involving 1904 neonates were included, revealing that SMOFlipid significantly reduced the cholestasis risk compared to other lipid emulsions.
- SMOFlipid offers a promising option for neonatal PN, particularly for reducing cholestasis in preterm infants and patent ductus arteriosus in extremely premature infants.

Availability of Data and Materials

All data included in this study are available upon request by contact with the corresponding author.

Author Contributions

TH and SY designed the research study. TH and JQH performed the literature search, inclusion and data collection. TH and DWR completed the bias assessment. SY provided help and advice throughout the research process. TH and DWR analyzed the data. TH and SY drafted the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0303.

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