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Effect of Low Lactose Formula on the Short-Term Outcomes of Neonatal Abstinence Syndrome: A Systematic Review

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Abstract

The use of low lactose formula (LLF) in term and near-term infants in infants with neonatal abstinence syndrome (NAS) has been increasing recently. However, the clinical evidence of such use is limited. Our aim in this paper was to systematically review the current literature about the use of LLF in infants with NAS. We searched PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, and Cochrane Database of Systematic Reviews for articles published between 2015 and 2020. Only randomized controlled trials, prospective, and retrospective studies. The risk of bias was assessed by using published tools appropriate for the study type. The certainty of the evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). Forty-one titles and/or abstracts were screened independently by 2 reviewers (MA and GA). After an indepth review, 4 studies answered the study question (1 randomized controlled trial (RCT), 2 retrospective studies, and 1 quality improvement study). A meta-analysis could not be completed due to the study type difference and how the outcomes were reported. The studies found no benefit to feeding LLF to infants with NAS regarding short-term outcomes (length of stay, duration, and need for pharmacological therapy and growth). Certainty in the evidence is low. In conclusion we found no beneficial effects regarding the need for pharmacological therapy, duration of pharmacological treatment, length of hospital stay, and growth of using LLF compared to the standard formula in infants with NAS.

Keywords

NAS, lactose free formula, lactose reduced formula, Morphine, Neonates, Neonatal growth

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Background

Newborns exposed to various opioids and other illicit substances in utero as part of a treatment program or addictive behavior are at risk of withdrawal and development of neonatal abstinence syndrome (NAS) due to discontinuation of exposure after birth. The type and intensity of withdrawal depend on many factors, including but not limited to the substance used, gestational age at birth, polysubstance abuse, breastfeeding, and genetic polymorphisms.¹ There has been a national increase in NAS incidence in the last decade. This incidence increase has resulted in a significant increase in the admissions to neonatal intensive care units and pediatric floors. A study that included 28 states reported a 300%

increase in NAS diagnoses from 1999 to 2013.² The care and extended hospital stay for each patient with NAS can cost the health care system up to \$53 400 US dollars.³ The rise in incidence and the resulting medical and financial burdens have been substantial driving

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factors for studying this condition's evaluation and management.⁴

Treatment of symptoms associated with NAS is generally based on a combination of pharmacological and non-pharmacological measures. Multiple pharmacological treatment protocols are followed by using morphine, methadone, or other medications.¹ However, starting medications for NAS treatment significantly increases the length of stay (LOS).⁵ For that reason, infants with mild to moderate NAS are most often managed with non-pharmacological measures, and most practices try to avoid pharmacological therapy. Research has recently focused on non-pharmacological factors, such as withdrawal scoring systems, rooming in with mother, minimizing surrounding environmental noise, nutritional management, gentle handling, on-demand feeding, swaddling, music and massage therapy, and skin-to-skin care with caregivers.^{1,6}

The literature has clearly shown that maternal breastmilk is beneficial for infants with NAS and significantly decreases the need for pharmacological therapy and the LOS.⁶ However, the evidence is less clear regarding the type of formula to be used if maternal breastmilk is unavailable or contraindicated. Given gastrointestinal (GI) system involvement of NAS, a recent trend has been observed of using low lactose formula (LLF) in infants with NAS.^{7,8} The non-evidence-supported use of these formulas is based on the hypothesis that partially hydrolyzed protein and low/free lactose carbohydrate decrease feeding intolerance and fussiness associated with NAS.

Methods

In this systematic review, we aimed to understand whether the use of LLF decreases the severity and the duration of NAS symptoms among term and near-term infants (≥ 35 weeks of gestation) with NAS compared with infants who received regular standard formula (RSF).

Inclusion Criteria

Studies that were eligible for inclusion included those that investigated the effect of using LLF in term or near-term infants with NAS diagnosis. In the included studies, the authors compared the outcomes regarding the need for pharmacological therapy for NAS, duration or cumulative dose of pharmacological treatment, length of hospital stay, and effect on growth between the infants who received LLF and those who used RSF. Randomized controlled trials (RCTs), cohort, case-control observational, and quality improvement studies were included in

the search. Case reports and case series were excluded. All written languages were accepted if an English abstract was provided.

Outcomes

The 4 outcomes analyzed in this systematic review included the need for pharmacological treatment, pharmacological treatment duration, length of hospitalization, and effect on growth if studied.

Literature Search

A medical librarian (KS) performed the search on December 22, 2020, of the available databases (PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, Cochrane Database of Systematic Reviews). A search method was performed from the year 2015 to 2020 utilizing the use of keywords and headings (("Neonatal Abstinence Syndrome/diet therapy") OR ("Neonatal Abstinence Syndrome" OR "neonatal abstinence syndrome") AND ("Infant Formula" OR "Enteral Nutrition" OR low lactose formula OR lactose-free formula OR protein partially hydrolyzed formula OR formula OR formula OR Feeds OR Feeding OR Enteral))) from the year of 2015 to 2020.

Study Selection and Extraction

Titles and abstracts were independently screened by 2 authors, MA and GA, who screened the full-text articles. Discrepancies were discussed and resolved after agreement with all investigators.

The Certainty of the Evidence, Risk of Bias Assessment, and Data Synthesis

GRADE was used to assess the overall certainty of the evidence.⁹ The Cochrane Collaboration Risk of Bias Tool was used to evaluate the RCT.¹⁰ A meta-analysis could not be completed due to the difference in the study type and statistical heterogeneity of the outcomes.

Results

Study Selection

Among 41 articles selected, 4 met the inclusion criteria: 2 cohort studies, 1 randomized controlled trial, and 1 quality improvement study, Figure 1.¹¹⁻¹⁴ The inclusion of 1 other study was ruled out after discussion and

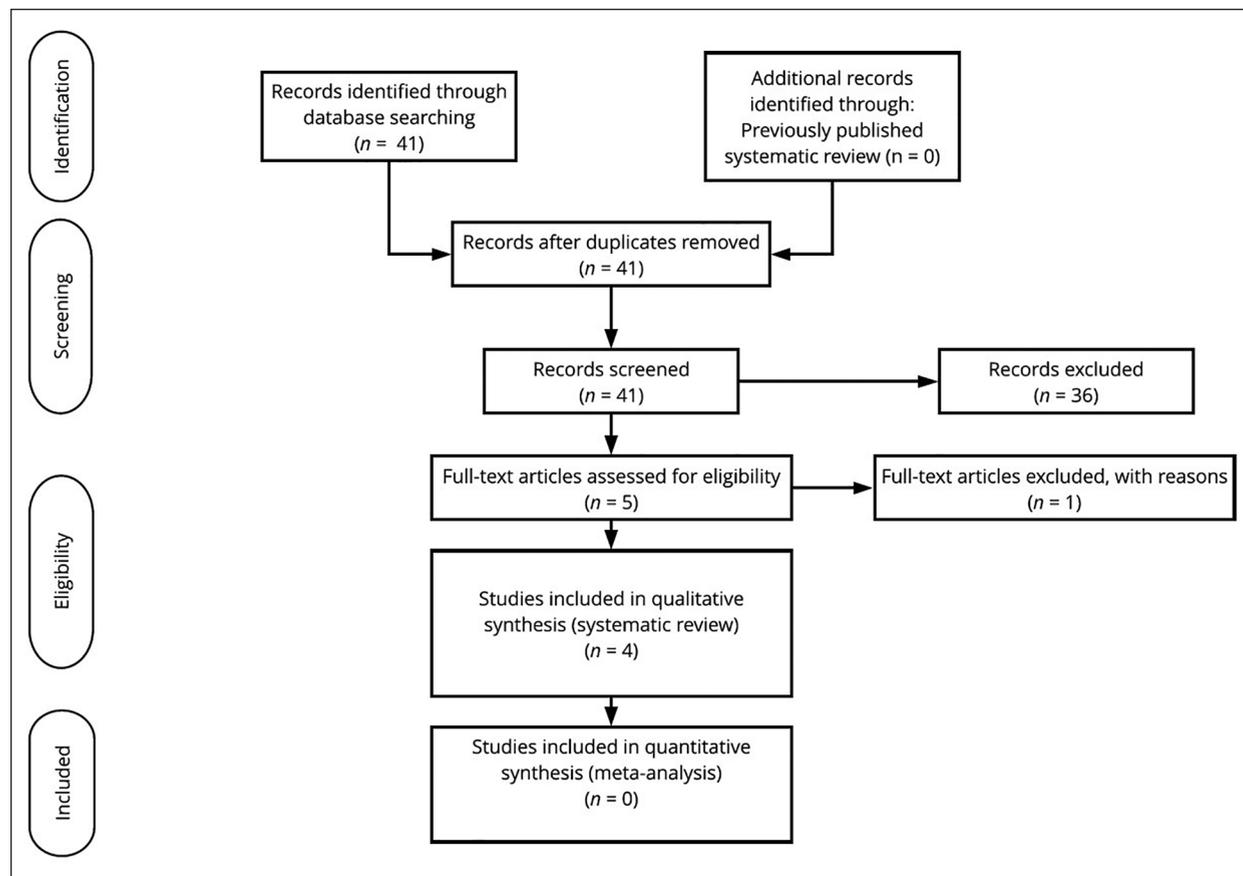


Figure 1. Prisma flow chart.

agreement between the authors.¹⁵ Study types, methodology, and limitations are shown in Table 1.

The 4 studies were from different institutions. The studies used 3-arm comparisons between LLF, RSF, and human milk. For this review's specific aim, we focused mainly on whether using LLF was more beneficial regarding short-term outcomes in infants with NAS. Alsaleem et al¹¹ and Pandey et al¹⁴ reported the type of LLF (Similac Sensitive (Abbott, Columbus, OH), and/or Enfamil Gentlease (Mead Johnson & Co., Glenview, IL)) that was used in the analysis. The other 2 studies did not specifically mention the kind of LLF used in the study population.^{12,13}

Morphine was the most common pharmacological therapy used in the studies included.^{11,12,14} Lembeck et al¹³ did not specifically mention which medication was used for treatment. The quality improvement project reported the use of morphine in most intensive care units, with a small number of newborns treated with methadone.¹² The pharmacological therapy needs assessment was based on either the pharmacological therapy duration or the cumulative dose of morphine

administered during the treatment duration. The risk of bias analysis for the RCT is shown in Table 2.

Results by Outcomes

Duration of pharmacological therapy. Three studies (Alsaleem et al, 2020; Lembeck et al, 2020; Pandey et al, 2020) measured the duration of treatment in infants with NAS (N=428). Alsaleem et al measured the duration of morphine sulfate (MSO₄) treatment in infants fed LLF versus RSF (n=110). After adjusting for the type of drug used by the mother, regular maternal involvement in prenatal care, maternal smoking status, and maximum scores prior to MSO₄ treatment, the intervention (LLF) was not different from RSF.¹¹ Lembeck et al¹³ measured the duration of therapy in infants fed LLF versus RSF (n=129). The authors found that the intervention (LLF) was not different from RSF. Pandey et al measured medication treatment duration in infants fed LLF versus infants fed RSF (n=69). The mean difference of treatment duration in days indicated the intervention (LLF) was not different from RSF.¹⁴

Table 1. Summary of the Type and Methodology of Included Studies.

	Alsaleem et al ¹¹	Kaplan et al ¹²	Lembeck et al ¹³	Pandey et al ¹⁴
Study design	Cohort	Quality improvement	Cohort	RCT
Subjects	NAS neonates ≥ 36 weeks	NAS neonates > 37 weeks	Neonates > 35 weeks	Neonates > 36 weeks
Exclusion criteria	1. Infants < 36 weeks 2. Presence of significant medical, surgical, or social condition other than NAS that could result in prolonged hospital stay	1. Exclusively breastfed infants	1. Neonates with NAS who were admitted to the NICU	1. Neonates with significant congenital anomalies or those with surgical and medical conditions that required the use of analgesics
Number of infants included	110	546	249	69
Controls	RSF	RSF	RSF	RSF
Outcomes reported	1. Need for pharmacological treatment 2. Duration of pharmacotherapy 3. First day of morphine treatment 4. Requirement of additional medication other than morphine 5. Length of hospital stay Morphine	1. Need for pharmacological treatment 2. Length of hospital stay 3. Treatment failure 4. Weight loss ($> 10\%$ within the first 7 days of life)	1. Need for pharmacological treatment 2. First day of morphine treatment 3. Length of hospital stay 4. Severity of symptoms 5. Growth	1. The cumulative dose of morphine during the first 14 days of life 2. Need of additional medication other than morphine 3. Duration of pharmacological treatment
Pharmacological agent used for treatment	Morphine	Morphine or methadone	Not reported	Morphine
LLF used	Gentleax or similac sensitive	Not reported	Not reported	Similac sensitive
Limitations	1. Selection bias (Cohort)	1. Selection bias (Cohort) 2. Did not account for all factors that drive LOS, treatment failure, or weight loss 3. Compliance issues	1. Selection bias (Cohort) 2. Only 63% of infants were exclusively fed 1 nutritional source	1. Study center changed NAS treatment guidelines midway through the study. Criteria for initiating pharmacologic therapy were made less stringent to allow initiation sooner based on NAS scores. This would likely affect both groups equally but remains noteworthy.

Abbreviations: NAS, neonatal abstinence syndrome; LOS, length of stay; RSF, regular standard formula; LLF, low lactose formula; NICU, neonatal intensive care unit.

Table 2. Risk of Bias Analysis for RCT Performed by Pandey et al¹⁴.

Risk of bias		
Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The randomization was done using a computer-generated random sequence (by research statistician DMS) (1:1) coupled with the stratified balanced blocked methodology. Stratification was done based on gender (male/female), gestational age (≤ 38 weeks/ > 38 weeks), and intrauterine exposure (polysubstance vs methadone or buprenorphine only).
Allocation concealment (selection bias)	Low risk	Allocation concealment was done using an opaque envelope.
Blinding of participants and personnel (performance bias)	Low risk	One member of the research team, not involved in clinical management, knew the group assignment. All other members of the research and clinical management teams remained blinded to group assignment throughout the study. Study formula preparation and masking were performed in a hospital-designated milk laboratory outside the normal nursery or NICU by hospital staff who were not involved in the study recruitment, study management, or data analysis. The study formula was sent to the bedside in identical transparent containers labeled "Study formula A" or "Study formula B." Parents, health care providers, and primary investigators were blinded to the study formula type.
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were objective.
Incomplete outcome data (attrition bias)	Unclear risk	Data analyzed per protocol. Two patients withdrew from each group with no explanation from the authors. Withdrawal unlikely to be related to study intervention.
Selective reporting (reporting bias)	Low risk	Pre-specified primary and secondary outcomes were reported as expected.
Other bias	Low risk	No additional sources of bias were noted.

The certainty of the evidence for the duration of treatment. The certainty of the body of evidence was very low. The body of evidence was assessed to have a risk of bias, inconsistency, and imprecision. The risk of bias was assessed as serious as 2 of the studies (Alsaleem et al¹¹ and Lembeck et al¹³) were retrospective cohorts, resulting in selection bias. Inconsistency was serious due to the heterogeneity of formulas used, calorie levels, and feeding type exclusivity. Imprecision was assessed as serious due to the low number of events.

Length of Stay

Three studies measured LOS in infants with NAS diagnosis (N=905).¹¹⁻¹³ Alsaleem et al¹¹ measured LOS in infants fed LLF versus RSF (n=110). After adjusting for the type of drug used by the mother, regular maternal involvement in prenatal care and inborn status, smoking status, and maximum scores prior to MSO₄ treatment, the intervention (LLF) was not different from RSF.^{11,13} Lembeck et al¹³ measured LOS in infants exclusively fed LLF versus those who were fed RSF. The

intervention (LLF) was not different from RSF. Kaplan et al measured LOS in infants fed low lactose high calorie (LL+HC) versus high lactose high calorie (HL+HC) versus low lactose low calorie (LL+LC) versus high lactose + low calorie (HL+LC) formula. The mean days indicated that the intervention (LL+HC) was less effective compared to HL+HC; however, the significance was not reported. LOS for LL+HC versus HL+HC was 16.6 and 14.8 days, respectively.¹²

The certainty of the evidence for LOS. The certainty of the body of evidence was very low. The body of evidence was assessed to have a serious risk of bias, serious inconsistency, and serious imprecision. The risk of bias was assessed as serious as 2 of the studies (Alsaleem et al¹¹ and Lembeck et al¹³) were retrospective cohorts, resulting in selection bias. Also, the risk of bias was serious as Kaplan et al's¹² study was a quality improvement study that did not report significance. Inconsistency was serious due to the heterogeneity of formulas used, calorie levels, and feeding type exclusivity. Imprecision was assessed as serious due to the low number of events.

Need for pharmacological therapy. Three studies (Alsaleem et al,¹¹ Lembeck et al,¹³ and Pandey et al¹⁴) measured the need for pharmacologic treatment in infants with NAS (N=428). Pandey et al¹⁴ indicated that the intervention (LLF) was not different compared to RSF. Cumulative morphine for the first 14 days was 20.7 ± 19.8 and 23 ± 23.5 mg for LLF and RSF, respectively. Alsaleem et al measured the need for pharmacological therapy in infants fed LLF versus standard term formula (n=110). After adjusting for the type of drug used by the mother, regular maternal involvement in prenatal care, smoking status, and maximum scores prior to MSO₄ treatment, the intervention (LLF) was not different from RSF.¹¹ In Lembeck et al,¹³ the authors found that the intervention (LLF) was not different from RSF.

The certainty of the evidence for pharmacological therapy.

The certainty of the body of evidence was very low based. The body of evidence was assessed to have a serious risk of bias, serious inconsistency, and serious imprecision. The risk of bias was assessed as serious, as 2 of the studies (Alsaleem et al¹¹ and Lembeck et al¹³) were retrospective cohorts, resulting in selection bias. Inconsistency was serious due to the heterogeneity of formulas used, calorie levels, and feeding type exclusivity. Imprecision was assessed as serious due to the low number of events.

Growth. One study (Lembeck et al) measured growth in infants exclusively fed LLF versus RSF (n=129). The authors reported that the intervention (LLF) was not different from RSF.¹³

The certainty of the evidence for growth. The certainty of the body of evidence was very low. The body of evidence was assessed to have a serious risk of bias and serious imprecision. The risk of bias was assessed as serious, as the study (Lembeck et al) was a retrospective cohort, resulting in selection bias 13. Imprecision was considered serious due to the low number of events. As only 1 study (Lembeck et al¹³) was identified to assess the effect of LLF on growth, consistency could not be assessed. More detailed information and statistical analysis of the included studies' outcomes are shown in Supplemental Table 1.

Discussion

Our goal was to evaluate the possible short-term beneficial effects of using LLF in term or near-term neonates with NAS in this review of the current literature. Our systematic review of 4 studies found no benefit regarding short-term outcomes (the need for pharmacological

therapy, duration of pharmacological treatment, LOS, and growth) using LLF compared to RSF in infants with NAS. Overall, the use of LLF did not improve the outcomes in neonates with NAS.

LLFs are different from RSF by having reduced or absent lactose content in addition to the presence of partially hydrolyzed protein components. Different brands are available on the market, such as Similac Sensitive, Enfamil Gentlease, and Gerber Good Start Gentle.¹⁶ The carbohydrate source in these formulas is usually derived from corn syrup solids compared to the standard human or cow milk that is mostly lactose derived. The reduced amount of lactose in these formulas can potentially interfere with the normal biological functions in neonates because lactose is an essential energy source in neonates and plays a role in calcium absorption and innate immunity.¹⁷⁻²⁰ Another potential drawback of these formulas is derived from the fact that the partially digested proteins do not have a similar trophic effect on the bioactive peptides and enzymes required for the normal digestive function in comparison to intact proteins present in humans or cows milk.^{21,22} Studies have shown that, in addition to the interference with these important biochemical functions, LLF has a bitter taste due to the partially hydrolyzed proteins when compared to RSF.²³

The LLF is usually an alternative to RSF for infants who experience feeding intolerance, severe colic symptoms, or reflux episodes. As NAS symptoms involve the GI system, these formulas have become an attractive option for infants with NAS to decrease GI symptom severity. Although evidence of such use lacked before 2019, the increasing trend of using these formulas has allowed researchers to evaluate this intervention's evidence-based practice. We found 2 cohort studies, 1 quality improvement project, and 1 double-controlled randomized trial performed recently that have shed light on the use of LLF in infants with NAS. We speculate that the results reported in this review originated from the pathophysiological mechanism associated with GI withdrawal symptoms seen in infants with NAS. Holzer showed that the effects of opioids on the GI tract are caused primarily by altering the acetylcholine neurotransmitter and receptor interaction. The reduced amount of lactose or the partially hydrolyzed proteins in LLF is unlikely to affect the signs and symptoms associated with the disturbance of the acetylcholine neurotransmitter pathway.²⁴

Although assessing the effect of maternal breast milk (MBM) on NAS outcomes was not the purpose of this review, we found that the authors of the 4 studies included in this systematic review found a consistent beneficial effect of MBM regarding the short-term outcomes (need for pharmacological therapy, duration of

pharmacological treatment, and hospital LOS). This observation is consistent with established evidence from previous studies showing favorable outcomes of infants with NAS who received human milk.^{25,26}

The strengths of this systematic review include the detailed literature search and assessment of the certainty of evidence using GRADE and the detailed analysis of the specific outcomes targeted in this review. Limitations include the small number of eligible studies and the significant heterogeneity between the included studies regarding outcomes reported. The lack of details about the percentage for the specific formula intake and the slightly different treatment protocols followed in each of the studies were additional limiting factors for which we could not control in this systematic review. Given the theoretical adverse effects of using LLF that may compromise calcium absorption and digestive function, we remain concerned about the lack of clear evidence for the use of LLF in infants with NAS.

Conclusion

From the limited evidence currently available, we did not find beneficial effects regarding the need for pharmacological therapy, duration of pharmacological treatment, LOS, and growth of using LLF compared to other standard formulas in infants with NAS. A conditional recommendation is made against LLF, as no beneficial effects were found in patients with NAS. This recommendation is based on expert opinion and a review of the current literature. The overall certainty of the evidence is low.

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Author Contributions

MA: Contributed to design, research, acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

GA: Contributed to conception, design, analysis, and interpretation; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work, ensuring integrity and accuracy.

JD: Contributed to analysis and interpretation; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work, ensuring integrity and accuracy.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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