Original Article

Effect of novel human milk oligosaccharides-based human milk fortifier containing lactoferrin, docosahexaenoic acid, and arachidonic acid on the growth of preterm infants with birth weight of 700–1800 g

Amitava Sengupta[1], Ajay Lal[2], Harsh Bhayana[3]

From [1]Director, Mother and Child Unit, Department of Neonatology and Pediatrics, Paras Hospitals, [2]Medical Director and Chief Neonatologist, Department of Neonatology, Lal Super-Speciality Hospital, Gurugram, [3]Medical Director and Chief Neonatologist, Department of Neonatology, Sonakshi Children Hospital, Hisar, Haryana, India

ABSTRACT

Background: Premature infants with low birth weight are at risk of growth failure and neurodevelopmental impairment. Human milk oligosaccharides (HMOs) are bioactive components of human milk that may enhance growth and development. The novel HMO-based human milk fortifier (HMoF), which also contains lactoferrin, docosahexaenoic acid (DHA), and arachidonic acid (ARA), can help provide a safer nutritional option for the growth of premature infants. **Materials and Methods:** We conducted a non-comparative observational study using data from multiple centers that used novel HMO-based HMF (HMoF) in premature infants (n=14) with birth weights of 700–1800 g. The primary outcome of the study was to assess tolerability (in terms of feed tolerance), and secondary outcomes included growth outcomes defined by weight, length, and head circumference during the stay in the NICU and at discharge. **Results:** A cohort consisting of 14 infants with a mean gestational age of 30.21±2.04 weeks and a birth weight of 1246.36±39.98 g comprised the study. During the study period, incidences of feed interruptions due to feed intolerability were nil, and no infant presented with any signs of adverse effects. The novel HMO-based HMF (HMoF)-fed infant cohort had a mean weight gain of 21.89±5.23 g/day, a mean length gain of 1.01±0.48 cm/week, and mean head circumference gain of 0.89±0.32 cm/week. The mean growth velocity recorded was 16.03±1.73 g/kg/day. **Conclusions:** Novel HMO-based HMF (HMoF) containing lactoferrin, DHA, and ARA demonstrated acceptable feed tolerance and weight gain without any clinically significant adverse effects. Data indicates that the novel HMoF containing lactoferrin, DHA, and ARA is a safe option for supporting the growth of preterm babies. However, further studies are needed to compare novel HMO-based HMF (HMoF) with standard HMF in a randomized controlled trial.

Key words: Growth, Human milk fortifier, Human milk oligosaccharides, Preterm babies

Premature infants with a low birth weight (<2500 g) are at risk of growth failure and neurodevelopmental impairment [1]. Adequate nutrition is essential for the optimal growth and development of these infants [2]. Human milk is considered the best source of nutrition for premature infants, as it contains bioactive components that may modulate immune function, intestinal microbiota, and brain development [3]. However, after a certain stage, human milk alone may not meet the nutritional needs of very low birth weight (<1500 g) infants, who would then require additional supplementation with a human milk fortifier (HMF) [4].

Human milk oligosaccharides (HMOs) are complex carbohydrates that are abundant in human milk but not in bovine milk or infant formula [5]. HMOs have been shown to have various beneficial effects on infant health, such as preventing infections, modulating inflammation, enhancing gut barrier function, and promoting brain development [6]. However, most commercially available HMFs are derived from bovine milk or whey protein and do not contain HMOs [7]. Therefore, there is a need to develop novel HMFs that contain HMOs and other bioactive components of human milk.

Recently, a novel HMO-based HMF (HMoF) containing lactoferrin, docosahexaenoic acid (DHA), and arachidonic acid (ARA) has been developed. This study has been conducted to provide evidence on the usage of a novel HMoF containing lactoferrin, DHA, and ARA and address concerns about feed tolerability and growth outcomes.

Access this article online	
Received - 22 January 2024 Initial Review - 03 February 2024 Accepted - 04 February 2024	Quick Response code
DOI: 10.32677/ijch.v10i11.4439	

Correspondence to: Dr Amitava Sengupta, Director, Mother and Child Unit, Department of Neonatology and Pediatrics, Paras Hospitals, Phase- I, C-1, Sushant Lok Rd, Sector 43, Gurugram-122002, Haryana, India. E-mail: amit19762000@yahoo.com" amit19762000@yahoo.com

MATERIALS AND METHODS

Study design and setting

A multicentric, non-comparative observational study was conducted on a cohort of 14 infants (10 males and 4 females) during the period between April 2023 and July 2023. Informed consent was obtained from the parents. The hospital ethics approval was obtained before the commencement of the study. Infants who were exclusively fed on human milk were chosen for the study.

Inclusion criteria

For the study involved, infants born with a birth weight of 700–1800 g and/or <36-week gestational age (GA), the intention to receive only human milk, and the ability to adhere to a feeding protocol based on the use of the mother's own milk or pasteurized donor milk wherever required.

A novel HMO-based HMF (HMoF), NiQu HMoF, containing lactoferrin, DHA, and ARA, was used to fortify expressed human breast milk or donor milk in a standard concentration of 1 g in 25 mL of human milk. Fortification was initiated when the enteral feed volume reached 100 mL/kg/day.

The novel HMO-based HMF (HMoF), NiQu HMoF, is devoid of maltodextrin, thus ensuring lower osmolality as compared to other bovine-based fortifiers. Human milk amylase breaks down maltodextrin, leading to the generation of osmotically active molecules, which results in hyperosmolality, leading to feed intolerance. Thus, maltodextrin-free human milk fortifiers prevent an increase in the osmolality of feeds [8].

Exclusion criteria

Exclusion criteria were defined by infants who had major congenital malformations or intestinal anomalies, sick neonates who could not tolerate enteral feeding, and infants who had received any other bovine-based formula or fortifier before enrolment in the study.

Primary outcome

Measures of the study included feed tolerability which was measured by recording events of feed intolerability including three or more episodes of emesis within a 24-h period, abdominal distention exceeding 2 cm or more, gastric residual volume exceeding 50% in two consecutive feeds, or blood-stained aspirate. All such events and other episodes which required feeding interruptions were recorded.

Secondary outcome

Measures included growth outcomes, including mean weight gain (g/day), mean length gain (cm/week), and mean gain in head circumference (cm/week). Weight was recorded daily, while length and head circumference were recorded once a week. Growth velocity (GV) (g/kg/day) was calculated using the exponential method. It was calculated as

GV=1000 × log (final weight/initial weight)/number of days [9]

Participants

The observational study included 14 premature infants who were assigned to receive HMO-based HMF (HMoF)-fortified human milk at the multiple centers participating in the study.

Data sources

The data for this observational study were obtained from the electronic or paper medical records of the centers. The data included demographic characteristics, clinical variables, growth measurements, and adverse events.

Ethical considerations

No incentives or compensation were provided to the participants. The hospital ethics approval was obtained before the commencement of the study.

RESULTS

A total of 14 infants were included in this observational study. Their baseline characteristics are shown in Table 1. The study outcomes in terms of primary and secondary outcome measures are shown in Table 2.

Table 1: Baseline characteristics of infants

Baseline characteristics of infants (n=14)	
Parameters	**n=14**
HMO-HMF (HMoF) group (n)	14
Gestational age (weeks) |mean±SD	30.21±2.04
Birth weight (g) |mean±SD	1,246.36±339.98
Age at initiation of fortification (days), mean±SD	12.14±7.79
Weight at initiation of fortification (g), mean±SD	1,246.79±287.87
Days of fortification (days) |mean±SD	16.79±6.97
Sex (male/female) |(%)	10/4 (71/29)
Lower segment cesarean section, n (%)	9 (64)
Sepsis, n (%)	7 (50)
Hyperbilirubinemia, n (%)	9 (64)
Ventilation, n (%)	5 (36)

SD: Standard deviation

Table 2: Study measure outcomes (n=14)

Study measure outcomes	
Weight gain/day (g)	21.89±5.23
Head circumference gain/week (cm)	0.89±0.32
Length gain/week (cm)	1.01±0.48
Growth velocity (g/kg/d)	16.03±1.73
Episodes of feed interruptions	0

DISCUSSION

This non-comparative observational study showed that novel HMO-based HMF (HMoF) containing lactoferrin, DHA, and ARA is well tolerated by preterm infants, with no reported clinically significant incidences of adverse effects. In addition, novel HMO-based HMF (HMoF) containing lactoferrin, DHA, and ARA improved the growth of premature infants at discharge.

Our findings are also in line with previous studies that have shown the beneficial effects of HMOs on the growth and development of term and preterm infants [6,10,11]. HMOs may enhance growth and development by modulating the gut microbiota, preventing infections, reducing inflammation, improving intestinal barrier function, and promoting brain development [6]. Lactoferrin, DHA, and ARA are also bioactive components of human milk that may have positive effects on the growth and development of premature infants by improving iron absorption, enhancing immune function, reducing oxidative stress, and supporting neurodevelopment [12-14].

However, our findings differ from some studies that have reported no effect of HMOs on the growth of term and preterm infants [15,16]. These discrepancies may be due to differences in study design, population characteristics, HMO composition, dosage and duration, confounding factors, and outcome measurements. For example, some studies used synthetic HMOs or isolated HMOs rather than natural HMOs or complex mixtures of HMOs [15,16]. Some studies also used lower doses or shorter durations of HMO supplementation than our study [16]. Moreover, some studies did not adjust for potential confounders such as GA, birth weight, sex, feeding mode, and co-morbidities [15].

The strengths of our study include the use of data from multiple centers that participated in an observational study, which reduced the uniformity and bias that may arise from single-center protocols. We also used standardized and validated methods to measure growth and development outcomes at discharge.

The limitations of our study include the non-comparative observational design, which precluded causal inference and increased the risk of confounding. We also had a small sample size and a short follow-up period, which limited the statistical power of our findings. Furthermore, we did not measure other outcomes that may be relevant for premature infants, such as infection rates, hospital re-admissions, neurodevelopmental impairment, and quality of life.

CONCLUSION

This non-comparative observational study suggests that novel HMO-based HMF (HMoF) containing lactoferrin, DHA, and ARA is well tolerated and improves the growth of premature infants with low birth weight at discharge. Further studies are needed to compare novel HMO-based HMF (HMoF) with standard HMF in a randomized controlled trial with a larger sample size and a longer follow-up period. The effect of novel HMO-based HMF (HMoF) on other outcomes such as infection rates, hospital readmissions, neurodevelopmental impairment, and quality of life should also be investigated. Novel HMO-based HMF (HMoF) may be a promising nutritional intervention for improving the health and development of premature infants.

ACKNOWLEDGMENT

We thank the infants and their parents or legal guardians who participated in this study. We also thank the staff of the NICU and the outpatient clinic who provided care and support to the infants.

REFERENCES

1. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, *et al.* Born too soon: The global epidemiology of 15 million preterm births. Reprod Health 2013;10 Suppl 1:S2.
2. Koletzko B, Poindexter B, Uauy R, editors. Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. Basel: Karger; 2014.
3. Martin CR, Ling PR, Blackburn GL. Review of infant feeding: Key features of breast milk and infant formula. Nutrients 2016;8:279.
4. ESPGHAN Committee on Nutrition, Arslanoglu S, Corpeleijn W, Moro G, Braegger C, Campoy C, *et al.* Donor human milk for preterm infants: current evidence and research directions. J Pediatr Gastroenterol Nutr 2013;57:535-42.
5. Bode L. Human milk oligosaccharides: Every baby needs a sugar mama. Glycobiology 2012;22:1147-62.
6. Ayechu-Muruzabal V, van Stigt AH, Mank M, Willemsen LE, Stahl B, Garssen J, *et al.* Diversity of human milk oligosaccharides and effects on early life immune development. Front Pediatr 2018;6:239.
7. Abrams SA, Schanler RJ, Lee ML, Rechtman DJ. Greater mortality and morbidity in extremely preterm infants fed a diet containing cow milk protein products. Breastfeed Med 2014;9:281-5.
8. De Curtis M, Candusso M, Pieltain C, Rigo J. Effect of fortification on the osmolality of human milk. Arch Dis Child Fetal Neonatal Ed 1999;81:F141-3.
9. Simon L, Hanf M, Frondas-Chauty A, Darmaun D, Rouger V, Gascoin G, *et al.* Neonatal growth velocity of preterm infants: The weight Z-score change versus Patel exponential model. PLoS One 2019;14:e0218746.
10. Puccio G, Alliet P, Cajozzo C, Janssens E, Corsello G, Sprenger N, *et al.* Effects of infant formula with human milk oligosaccharides on growth and morbidity: A randomized multicenter trial. J Pediatr Gastroenterol Nutr 2017;64:624-31.
11. Marriage BJ, Buck RH, Goehring KC, Oliver JS, Williams JA. Infants Fed a lower calorie formula with 2'FL show growth and 2'FL uptake like breast-fed infants. J Pediatr Gastroenterol Nutr 2015;61:649-58.
12. Lönnerdal B. Lactoferrin in human milk: Its role in iron absorption and protection against enteric infections in the newborn infant. Arch Dis Child 1980;55:417-21.
13. Innis SM. Dietary omega 3 fatty acids and the developing brain. Brain Res 2008;1237:35-43.
14. Carlson SE, Colombo J, Gajewski BJ, Gustafson KM, Mundy D, Yeast J, *et al.* DHA supplementation and pregnancy outcomes. Am J Clin Nutr 2013;97:808-15.
15. Berger B, Porta N, Foata F, Grathwohl D, Delley M, Moine D, *et al.* Linking human milk oligosaccharides, infant fecal community types, and later risk to require antibiotics. mBio 2020;11:e03196-19.
16. Goehring KC, Marriage BJ, Oliver JS, Wilder JA, Barrett EG, Buck RH. Similar to those who are breastfed, infants fed a formula containing 2'-fucosyllactose have lower inflammatory cytokines in a randomized controlled trial. J Nutr 2016;146:2559-66.

Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Sengupta A, Lal A, Bhayana H. Effect of novel human milk oligosaccharides-based human milk fortifier containing lactoferrin, docosahexaenoic acid, and arachidonic acid on the growth of preterm infants with birth weight of 700–1800 g. Indian J Child Health. 2023; 10(11):142-144.