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Original Research Article

An observational study to assess the effect of novel human milk oligosaccharides based human milk fortifier containing lactoferrin, docosahexaenoic acid and arachidonic acid on growth of preterm infants with birth weight of 700-1800 gm

Arvin[1]*, Jatinder Singh[2], Aditi[3], Amandeep Kaur[2]

[1]Punjab Institute of Medical Sciences, Jalandhar, India
[2]Department of Pediatrics, Punjab Institute of Medical Sciences, Jalandhar, India
[3]Department of Community Medicine, Government medical college, Amritsar, India

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***Correspondence:**
Dr. Arvin,
E-mail: arvink206@gmail.com

ABSTRACT

Background: Preterm infants with low birth weight (LBW) have increased nutritional needs and are at high risk of postnatal growth failure. While human milk is the optimal source of nutrition, it often requires fortification to meet the demands of preterm infants. Novel human milk fortifiers enriched with human milk oligosaccharides (HMOs), lactoferrin, docosahexaenoic acid (DHA), and arachidonic acid (ARA) may offer added benefits in supporting growth and feeding tolerance.
Methods: This observational study was conducted in the neonatal intensive care unit of a tertiary care hospital over one year. Preterm infants with birth weight 700-1800 g and/or gestational age <36 weeks, intended to receive exclusive human milk, were enrolled. A novel HMO-based human milk fortifier containing lactoferrin, DHA, and ARA was initiated once enteral feeds reached 100 ml/kg/day. Growth parameters including weight, length, and head circumference were monitored, along with feeding tolerance and clinical outcomes. Descriptive statistical analysis was performed.
Results: A total of 100 preterm infants were included. The mean gestational age was 32.68±2.83 weeks and mean birth weight was 1430.11±270.02 g. Fortification was initiated at a mean age of 9.42±1.44 days. The mean weight gain was 21±11 g/day, mean length gain was 1±0.1 cm/day, and mean head circumference gain was 0.73±0.05 cm/day. The fortifier was well tolerated, with no significant adverse effects observed.
Conclusions: The novel HMO-based human milk fortifier was safe, well tolerated, and associated with satisfactory growth in preterm infants, suggesting its potential role in optimizing neonatal nutrition.

Keywords: Preterm infants, Human milk oligosaccharides, Human milk fortifier, Lactoferrin

INTRODUCTION

Preterm birth, defined as birth occurring before 37 weeks of gestation, is a significant global health concern, contributing to high rates of neonatal morbidity and mortality. Preterm infants, particularly those with a birth weight between 700 and 1800 grams, are at increased risk of growth failure, developmental delays, and various health complications due to their immature physiological systems. Infants with very LBW (VLBW, <1500g), face significant nutritional challenges that can impact their short-term survival and long-term developmental outcomes. Human milk is widely recognized as the optimal nutrition for these vulnerable infants, providing

numerous benefits including improved feeding tolerance, reduced risk of necrotizing enterocolitis, and enhanced neurodevelopmental outcomes. However, human milk alone may not meet the elevated nutritional requirements of preterm infants, necessitating fortification to support optimal growth and development.

HMOs are complex carbohydrates naturally present in human milk that play crucial roles in infant health, including prebiotic effects, antimicrobial activities, and support for immune system development. Recent advancements in nutritional science have led to the development of novel human milk fortifiers that incorporate HMOs along with other bioactive components such as lactoferrin, DHA, and ARA.

Lactoferrin, an iron-binding glycoprotein found naturally in human milk, has demonstrated antimicrobial, immunomodulatory, and anti-inflammatory properties.[1] DHA and ARA are long-chain polyunsaturated fatty acids essential for optimal brain and retinal development, particularly crucial for preterm infants who miss the significant accretion of these fatty acids that typically occurs in the third trimester of pregnancy.[2]

While the individual benefits of HMOs, lactoferrin, DHA, and ARA have been studied, there is limited research on the combined effects of these components in a human milk fortifier specifically designed for preterm infants. This observational study aims to investigate the impact of a novel HMO-based human milk fortifier containing lactoferrin, DHA, and ARA on the growth of preterm infants with birth weights ranging from 700 to 1800 grams.

The primary objective of this study includes evaluating feeding tolerance, incidence of necrotizing enterocolitis, late-onset sepsis, and other common morbidities associated with prematurity and the secondary objective is to assess the effect of this fortifier on weight gain and linear growth.

By examining the potential synergistic effects of these bioactive components in a single fortifier, this study aims to contribute valuable insights into optimizing nutritional support for preterm infants. The findings may inform future nutritional practices in neonatal intensive care units and potentially improve short-term and long-term outcomes for this vulnerable population.

Aims and objectives

Aim and objectives were to study the effect of novel HMO based human milk fortifier containing Lactoferrin/DHA/ARA in terms of feed tolerability in preterm infants and to study the effect of weight gain at regular fortification (Feed volume of 100ml/kg/day) on preterm infants with novel HMO based human milk fortifier containing Lactoferrin/DHA/ARA.

METHODS

Study setting

The present study was conducted in neonatal intensive care unit of Department of Pediatrics, Punjab institute of medical sciences, Jalandhar which is level 2A Nic and is NNF accredited.

Study population

Preterm infants presenting to NICU.

Inclusion criteria

Birth weight 700-1800 g and/or <36 weeks gestational age (GA), intention to receive only human milk and ability to adhere to a feeding protocol based on the use of mother's own milk or pasteurized donor milk wherever required (however it wasn't used in study) were included.

Exclusion criteria

Major congenital malformations or intestinal anomaly, sick neonates who cannot tolerate enteral feeding and infants who have received any other bovine-based formula/fortifier prior to enrolment in study were excluded.

Study design

This was an observational study

Study period

One year i.e. 3rd January 2025 to 2nd January 2026.

Sample size

The sample size was calculated using following formulae

$N=(Z\alpha/2)^2 *(SD)^2/d^2$

Where; N-Sample size; Zα/2–Z value at 5% error (1.96); SD=average standard deviation of the growth velocity of newborn(=1.73g/kg/d) and; d- precision (0.5 g/Kg/day)

$N=(1.96)^2*(1.73)^2/(0.5)^2=30$ (approx)

Sampling technique

Convenience sampling was used wherein all patients reporting to NICU will be subjected to inclusion and exclusion criteria and included in the study based on it.

Study tools

A pre-structured questionnaire, pre tested, pre validated was used for data collection. After completing the survey

tool, the anthropometric measurements were done according to the following standard procedure:

Length

The child is placed supine and the mother/assistant was asked to keep the vertex or top of head snugly touching a hard flat surface, so that the external auditory meatus and lower margins of the orbits are aligned perpendicular to the table. The legs were fully extended by pressing over the knees and feet are kept vertical at 90 degrees. Cardboards were placed on the head end and foot end of the infant and the distance between them was measured by a measuring tape.

Weight

It was be ensured that the scale is placed on a firm flat surface. The child's mother/assistant will be asked to remove their footwear (shoes, slippers, sandals etc) and step onto the scale with one foot on each side. The mother/assistant was then asked to hold the baby and the weight was recorded again. The weight of the baby was calculated by deducting the weight of the mother/assistant from the final weight.

Head circumference

The parent or caregiver was asked to assist by holding the infant's head steady whilst sitting up and provide comfort to the infant. If poor head control, it was measured with infant lying down. The tape was placed evenly around the head anchoring it just above the ears and eyebrows and around the fullest protuberance (largest circumference) of the skull at the back at the back of the child's head. The tape is pulled so it fits snugly against the infant's skull, compressing the hair and skin.

Composition of HMO

NiQu HMoF is a fortifier designed specifically for the preterm and LBW babies. It is closest to human milk, human milk sugars such as HMOs, human milk protein such as Lactoferrin, essential fatty acids such as DHA / ARA, all essential vitamins and minerals, and 30% protein content.

Table 1: Composition of HMO.

Nutrients	Units	Per 1 gm sachet	Per serve of 100 ml (4 gm powder+100 ml human milk)
Energy	Kcal	4.1	84.4
	KJ	17.3	355
Protein	G	0.30	2.8
Lactoferrin	Mcg	50	
Fat	G	0.15	4.1
Carbohydrates	G	0.40	8.9
2'Fucosyllactose (2'FL)	Mg	5.30	295
Lacto-N-Tetraose (LNnT)	Mg	2.60	44.7
Sugar (Sucrose)	G	0.0	0
DHA	Mg	2.00	19.2
ARA	Mg	2.00	24.5
Vitamin A	mcg RE	140	574
Vitamin D2	Mcg	4.0	16.2
Vitamin E	mcg TE	372	1488
Vitamin K	Mcg	1.00	6.0
Vitamin C	Mg	5.00	24.4
Thiamine	Mcg	20.0	88.9
Riboflavin	Mcg	25.0	127
Niacin	Mcg	210	1050
Pantothenic acid	Mcg	88.0	582
Vitamin B6	Mcg	24.0	102.2
Biotin	Mcg	0.50	2.5
Vitamin B12	Mcg	0.05	0.2
Folic acid	Mcg	13.0	55
Sodium	Mg	4.50	46
Potassium	Mg	4.00	66
Calcium	Mg	15.0	85
Chloride	Mg	18.0	130
Phosphorus	Mg	8.00	47
Magnesium	Mg	2.00	11
Iron	Mg	0.40	1.7

Continued.

Nutrients	Units	Per 1 gm sachet	Per serve of 100 ml (4 gm powder+100 ml human milk)
Zinc	Mcg	190.00	760
Copper	Mcg	12.00	86
Manganese	Mcg	1.00	4.4
Iodine	Mcg	0.20	18.6
Inositol	Mg	0.84	3.4
Taurine	Mg	0.37	5.5

Ethical considerations

Prior to the commencement of the study, approval from institutional ethics committee was taken and written informed consent was taken from every primary caregiver. No personal identifier was used to maintain confidentiality at all levels. The data collected was not shared with anyone inside or outside the institution.

Data analysis

Data was compiled and analyzed using SPSS ver. 26.0. For categorical data frequency and percentages were calculated. For continuous data, mean±standard deviation and median (95% confidence interval) were calculated whichever relevant. The association will be established using Chi-Square Test and strength of the association were assessed by calculating Odds Ratio for categorical data.

RESULTS

The majority of neonates (94%) were born at a gestational age greater than 28 weeks, while only 6% were born before 28 weeks of gestation. This indicates that most participants belonged to the late preterm or near-term category. The relatively smaller proportion of extremely preterm infants reflects the overall gestational maturity of the study population.

Out of 100 neonates, 52% were female and 48% were male. The distribution shows a nearly equal representation of both genders in the study. This balanced gender distribution minimizes gender-related bias in the interpretation of outcomes.

Table 2 presents the mode of delivery among the study participants. A majority of neonates (76%) were delivered by lower segment cesarean section (LSCS), while 24% were delivered through normal vaginal delivery (NVD). The higher rate of LSCS may be attributed to obstetric indications commonly associated with preterm or low-birth-weight deliveries. This highlights the increased need for operative delivery in high-risk pregnancies.

Table 3 describes the various medical conditions observed among the study participants. Jaundice requiring phototherapy was the most common condition, affecting 64% of neonates. Ventilation or CPAP support was required in 36% of cases, while sepsis was noted in 26%. Less frequent complications included seizures (2%) and intracranial hemorrhage (1%), indicating that severe neurological complications were relatively uncommon.

Table 4 illustrates the duration of total parenteral nutrition (TPN) among the study participants. Most neonates required TPN support for a limited number of days, indicating early transition to enteral feeding. The distribution suggests that prolonged dependence on TPN was uncommon. This reflects effective nutritional advancement and gastrointestinal tolerance in the majority of neonates.

Table 5 presents the distribution of neonates based on birth weight categories. A majority (62%) were classified as LBW, followed by 35% as very LBW (VLBW). Only 3% of neonates fell into the extremely LBW (ELBW) category. This distribution highlights that most participants were within the LBW and VLBW ranges.

Table 6 summarizes the baseline characteristics of the neonates included in the study. The mean gestational age was 32.68±2.83 weeks, and the mean birth weight was 1430.11±270.02 grams.

The mean age and weight at commencement of human milk oligosaccharide (HMO) supplementation were 9.42±1.44 days and 1413.99±230.30 grams, respectively. The average amount of oral feed was 174.71±15.92 ml, indicating adequate feeding tolerance at initiation.

Table 7 depicts the growth outcomes observed in the study population. The mean total weight gain was 424±236 grams, with an average daily weight gain of 21±11 grams.

The mean length gain per day was 1±0.1 cm, while the mean head circumference gain per day was 0.73±0.05 cm. These findings suggest satisfactory growth performance during the study period. Mean age for commencement of HMO was 9.5 days (IQR 8-10) (Figure 1) while mean weight was 1434.33g (IQR 1299-1630) (Figure 2).

According to Figure 3 the mean weight gain per day was 43 g with an IQR of 40-47.

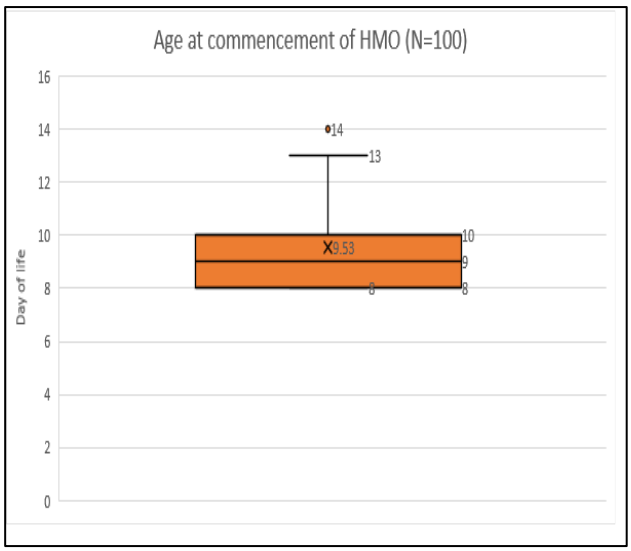

Figure 1: Age at commencement of HMO.

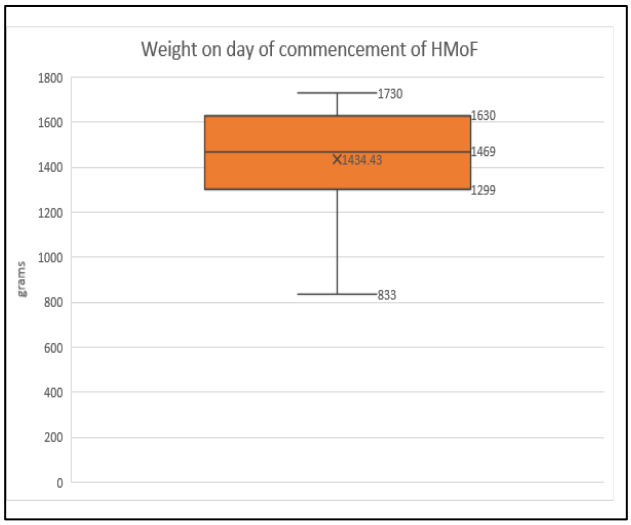

Figure 2: Weight on the day of commencement of HMO.

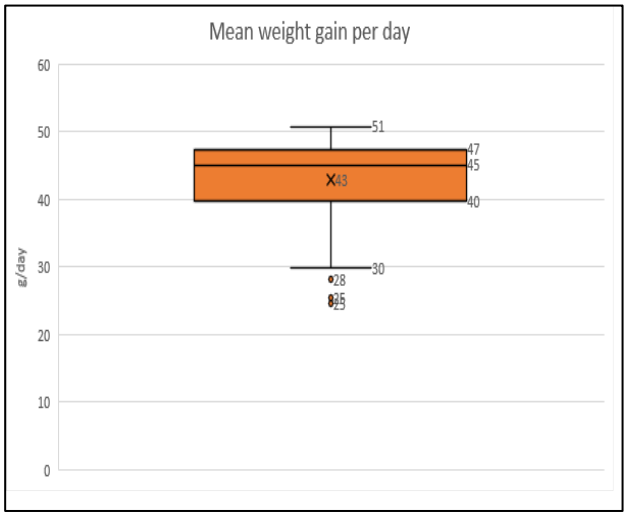

Figure 3: Mean weight gain per day, (n=100).

Table 2: Distribution of study participants according to their mode of delivery, (n=100).

Mode of delivery	N
NVD	24
LSCS	76
Total	100

Table 3: Distribution of study participants according to their medical history, (n=100).

Variables	N
Ventilation/CPAP	36
Sepsis	26
Intracranial hemorrhage	1
Seizures	2
Jaundice requiring phototherapy	64

Table 4: Distribution of study participants according to days spent on TPN, (n=100).

No. of days	N
2	3
3	2
Total	100

Table 5: Distribution of study participants according to birth weight, (n=100).

Birth weight (g)	N
<2500 (LBW)	62
<1500 (VLBW)	35
<1000 (ELBW)	3

Table 6: Baseline characteristics.

Parameters	Mean±SD
Gestational age (weeks)	32.68±2.83
Birth weight (g)	1430.11±270.02
Age on commencement of HMO (in days)	9.42±1.44
Wt on commencement of HMO	1413.99±230.30
Amount of oral feed (ml)	174.71±15.92

Table 7: Growth parameters, (n=100).

Parameters	Mean±SD
Total weight gain (g)	424±236
Mean weight gain/day (g)	21±11
Mean length gain/day (cm)	1±0.1
Mean gain in head circumference/day (cm)	0.73±0.05

DISCUSSION

Demographic and clinical characteristics

Study population (n=100) predominantly consisted of infants born after 28 weeks gestation (94%), with a mean

gestational age of 32.68±2.83 weeks. Gender distribution relatively balanced, with 52% female, 48% male infants. High rate of cesarean delivery (76%) compared to normal vaginal delivery (24%) aligns with findings from other studies of preterm infants. A multicenter study by Malloy et al reported increased rates of cesarean deliveries in preterm infants, particularly those with VLBW.[3]

Birth weight and prematurity

The birth weight distribution reveals a significant proportion of LBW infants (62%), with 35% classified as VLBW and 3% as ELBW. The mean birth weight was 1430.11±270.02 g. This distribution is particularly relevant given that VLBW infants are at higher risk for feeding intolerance and necrotizing enterocolitis (NEC). Korpela et al demonstrated that early human milk feeding in this population can significantly reduce the risk of NEC and improve outcomes.[4] Similar findings were reported by Cristofalo et al who emphasized the protective effects of human milk in VLBW infants.[5]

Clinical complications and interventions

Medical history data indicates a high prevalence of complications, with 84% of infants experiencing some form of medical event. Most common complications were jaundice requiring phototherapy (64%), followed by ventilation/ CPAP support (36%) and sepsis (26%). Relatively high rate of respiratory support aligns with literature on preterm infants, where respiratory morbidity remains a significant challenge, as documented by Sweet et al and confirmed in recent systematic review by Staub et al.[6,7]

Growth parameters and HMO supplementation

Anthropometric data shows encouraging growth outcomes with HMO supplementation. Mean weight gain of 21±11 g/day falls within recommended range for preterm infant growth, as established by Ehrenkranz et al.[8] Timing of HMO initiation occurred at a mean age of 9.42±1.44 days, when infants had reached mean weight of 1413.99±230.30 g. Linear growth (1±0.1 cm/day) and head circumference gain (0.73±0.05 cm/day) consistent with optimal growth trajectories for preterm infants.[9]

These growth rates compare favorably with those reported by Puccio et al in their study of HMO supplementation.[10] The mean oral feed volume of 174.71±15.92 ml suggests good feeding tolerance, which is particularly noteworthy given the high proportion of VLBW infants in the cohort. Recent work by Bode et al has further elucidated the mechanisms by which HMOs may contribute to improved feeding tolerance.[11]

Limitations

Being an observational study without a control group, causal relationships between the HMO-based human milk fortifier and growth outcomes cannot be definitively established. The use of convenience sampling from a single tertiary care NICU may limit the generalizability of the results to other settings or populations. The relatively small sample size and short duration of follow up restricted assessment of long-term growth and neurodevelopmental outcomes. Additionally, potential confounding factors such as variations in clinical management, maternal milk composition, and underlying neonatal morbidities could not be completely controlled, which may have influenced observed growth outcomes

CONCLUSION

The present study demonstrates that the novel HMO-based human milk fortifier containing lactoferrin, DHA, and ARA was safe, well tolerated, and associated with satisfactory growth outcomes among preterm infants with birth weights between 700-1800 g. The findings suggest that fortification of human milk with bioactive components may support improved nutritional adequacy and feeding tolerance in this vulnerable population. By providing real world clinical evidence from a neonatal intensive care setting, this study contributes to the growing body of knowledge on advanced human milk fortification strategies and highlights the potential role of HMO-based fortifiers in optimizing nutritional care for preterm infants.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee (No.PIMS/IEC/25/03)

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