Original Article

Effect of 100% human milk-derived fortifier on growth of premature infants with birth weight of 1000–1500 g

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ABSTRACT

Background: Preterm birth has the highest risk of perinatal morbidity and mortality. Nutrition plays a key role in the growth and development of a preterm infant. Fortification of expressed breast milk is followed to provide an optimal nutrition and a faster catch up growth. The new 100% human milk-derived fortifier (HMDF) can help in providing a safe nutritional option for a premature infant. **Objective:** The objective of the study was to assess the feed tolerance and impact of a new 100% HMDF on growth outcomes of preterm infants. **Materials and Methods:** In a single-center study, exclusively human milk-fed preterm infants (1000–1500 g birth weight) were chosen to receive human milk fortified with a new 100% HMDF. The fortifier was initiated when the enteral feed volume reached 100 ml/kg/day and was administered until discharge. The primary outcome of the study was to assess feed tolerance and the secondary endpoints included growth parameters. **Results:** The cohort study comprised 13 infants with a mean gestational age of 31.64±2.2 weeks and birth weight of 1314.62±110.1 g. During the study period, feed interruptions were nil and none of the infants showed any adverse events of clinical significance. Growth outcomes recorded at the end of the study period showed a mean weight gain of 25.97±7.7 g/day, mean length gain of 0.32±0.23 cm/week, and mean head circumference gain of 0.39±0.20 cm/week. The mean weight growth velocity of the infants was 18.37±5.1 g/kg/day. **Conclusion:** Preterm infants who received a new 100% HMDF demonstrated feed tolerance and weight gain without any clinically significant record of adverse events. The findings indicate that the new HMDF is a safe option for providing an exclusive human milk-based diet. However, a study with a larger study population may be required to reinforce the findings of this study.

Key words: *Fortifier, Human milk, Premature infants*

Nutrition requirement for a premature infant is greater than that of a term infant [1-3]. Richness of bioactive proteins in human milk provides unmatched benefits to the growth and development of a prematurely born infant. It is a well-recognized fact that human milk's benefits extend beyond nutrition by reducing the risk for both early and late complications for the newborn [4]. Achieving the nutrition goal for a premature infant is the need of the hour in the neonatal intensive care unit (NICU) [4]. Raw human milk is insufficient to meet the nutritional demands of a very low birth weight (VLBW) preterm infant; studies have shown that feeding of unfortified human milk resulted in inadequate weight gain and growth [5-7].

Fortifying human milk aids in providing essential macronutrients to meet the demand of VLBW infant. At present, two types of fortifiers are available in India which are bovine milk based or human milk based [8]. Human milk comprises 60% whey and 40% casein proteins, which is in contrast to bovine milk, where whey is present in nominal quantity (18%) and casein in major quantity (80%) which makes bovine milk-based fortifiers (BMBFs) to result in the formation of firm coagulum – making it difficult for the preterm infants to digest [9,10].

Evidence suggests that for every increase in 10% bovine milk-based diet is associated with an 11.8% increase in the risk of necrotizing enterocolitis (NEC), there is 21% increase in the risk of surgical NEC and 17.9% increase in the risk of sepsis [3]. It is also suggested that risk of NEC reduces substantially when mother's own milk or pasteurized donor human milk is used for preterm infants [11]. Following exclusively human milk-based diet (EHMD) regimen is achievable using a fortifier which is derived completely from the human milk [3]. Till recently, availability of 100% human milk-derived fortifiers (HMDFs) was limited only to the USA. For the 1st time in India and Asia, a complete HMDF is available to ensure the EHMD. We planned this study to provide the evidence on 100% human milk fortifier (HMF) in India.

MATERIALS AND METHODS

A single-center, descriptive cohort study was conducted among 13 infants (6 males and 7 females) over a period of 4 months

between September 2018 and December 2018. Informed consent was obtained from the parents. The Institutional Ethics Approval was obtained before commencement of the study. Infants who were exclusively fed on human milk were chosen for the study, to ensure EHMD.

Inclusion criteria for the study were birth weight of 1000–1500 g and/or <34 weeks' gestational age (GA), intention to receive only human milk, and the ability to adhere to a feeding protocol based on the use of mother's own milk. The infants with major congenital gastrointestinal malformations or infants, who had received any bovine-based formula fortifier before enrollment in the study, were excluded from the study.

As per the standard protocol, total parenteral nutrition was started on day 1 and continued till infants tolerated more than 50% of the requirements orally. Oral feeds were initiated on day 2; all infants received mother's own milk. HMF was initiated when the enteral feed volume reached 100 mL/kg/day. Fortified feeds were stopped at discharge. Infants were discharged based on the following criteria: 34 weeks' corrected gestation, breastfeeding adequately or tolerating all requirements orally, and weighing at least 1.6 kg.

Neolact Mother's Milk Fortifier®, 100% HMDF, was used in the current study. Since hyperosmolar preparations (>400 mOsm/kg) are associated with NEC, the fortifier has been designed (maltodextrin free) to maintain lower osmolality than the bovine-based HMF [12]. The enzyme amylase, that is present in human milk, breaks down maltodextrin, resulting in a higher number of osmotically active molecules, which consequently increases osmolality. Thus, a maltodextrin-free fortifier prevents hyperosmolality [13,14].

Primary outcome measure of the study was feed intolerance which was measured as events comprising 3 or more episodes of emesis within a 24-h period, abdominal distention is exceeding 2 cm or more, or gastric residual volume exceeding 50%. The number of feeding episodes that required interruptions was also recorded [15]. Secondary outcome measure was growth outcome which comprised mean gain in weight, length, and head circumference at the end of the study. Weight was measured daily, while length and head circumference were measured weekly until discharge. The growth velocity (g/kg/day) during the study period was also calculated. It was calculated as $\frac{\left[\left(W_{n+1}-W_n\right)\times 1000\right]}{\left[\left(W_n+W_{n+1}\right)/2\right]}$ in daily increments until discharge, where W_n=Weight in grams on day "n" and W_{n+1}=Weight in grams on the following day [16].

RESULTS

A total of 13 infants were enrolled during the study period. The mean GA and birth weight of the infants were 31.64±2.2 weeks and 1314.62±110.1 g, respectively. Table 1 enumerates the baseline characteristics that were similar across the study subjects. The mean age at the initiation of fortification was 10.23±4.9 days, and the mean weight was 1273.85±100.8 g.

The mean feed volume was 118.75±15.8 mL/kg. No episodes of feed interruptions were reported and 100% HMDF was well tolerated by all the infants. The study outcomes at the end of the study are presented in Table 2. Further, a mean growth velocity of 18.37±5.1 g/kg/day was observed across the study population. The absence of feed interruptions and linear growth velocity indicates that safe growth was achieved with the HMDF, without compromising on growth markers.

DISCUSSION

The number of premature newborns continues to rise in India and so is the importance of nutrition to ensure the intact survival [17]. Bovine milk has been the source for the multinutrient fortifiers [18]. Recently, using lactoengineering techniques, multinutrient fortifiers have been derived from human milk instead of bovine milk [3]. Since exposure to commercial formula feeds is thought to increase the morbidities including NEC, multicomponent HMDF has been used to minimize exposure to bovine products. HMDF is introduced, once tolerance of feeds at a volume greater than trophic feeds is demonstrated. The supplementation with HMDF is continued until around 34 weeks when transition to a post-discharge transitional formula or a term formula is made. There are very few studies available on the use of HMDF.

Cristofalo *et al*. studied infants with birth weight of ≤1250 g for whom mother's milk was not available. Infants were randomized into two groups. One group received donor HMF with HMDF and the other group received formula feeds. Results from this study demonstrated a significant reduction in the number of days of parenteral nutrition and zero surgical NEC cases in HMDF group as compared to formula feed group which had more days in parenteral nutrition and four cases of surgical NEC [19].

Sullivan *et al*. studied the effects of fortification with HMDF versus bovine milk-based fortifiers (BMBFs) in VLBW infants

Table 1: Baseline characteristics of the study subjects

Parameter	n=13
Birth weight (g), mean±SD	1314.62±110.1
Gestational age (weeks), mean±SD	31.64±2.2
Male/female, n (%)	6/7 (46/54)
Lower segment cesarean section, n (%)	13 (100)
Continuous positive airway pressure, n (%)	11 (85)
Sepsis, n (%)	3 (23)
Intracranial hemorrhage, n (%)	3 (23)
Hyperbilirubinemia, n (%)	13 (100)
Total parenteral nutrition (days), mean±SD	3.31±3.4
Age at initiation of fortification (days), mean±SD	10.23±4.9
Weight at initiation of fortification (g), mean±SD	1273.85±100.8

SD: Standard deviation

Table 2: Study outcomes (n=13)

Parameter	Mean±standard deviation
Weight gain/day (g)	25.97±7.7
Head circumference gain/week (cm)	0.39±0.20
Length gain/week (cm)	0.32±0.23
Growth velocity (g/kg/d)	18.37±5.1
Episodes of feed interruptions	0

with birth weight of <1250 g (n=207), results demonstrated that HMDF group had a decrease in the likelihood of parenteral nutrition with a significant reduction in NEC (6% vs. 16%, p=0.02). HMDF achieved EHMD with 50% reduction in NEC and 90% reduction in surgical NEC when compared with the BMBF group. Authors concluded that HMDF group had 77% reduction in the chances of developing NEC versus the BMBF [3].

Ganapathy *et al*. assessed the cost-effectiveness of feeding extremely premature infants with expressed breast milk fortified with BMBF versus 100% HMDF. Results from this study showed that there was a significant reduction of overall costs of NICU stay with HMDF group when compared with BMBF. Incidence of both medical and surgical NEC was low with HMDF and hence cost reductions of medical NEC by 2.5 times and surgical NEC by 7 times when compared with BMBF [20].

Our study revealed that an EHMD fortified with 100% HMDF was well tolerated by preterm infants and was beneficial. Since the early research results of studies are promising, further studies and large trials are required to establish the potential benefits of HMDF. A recent consensus statement by the panel on "Human milk in feeding premature infants" concluded that HMDFs that are currently available are probably of a better quality than cow's milk-based fortifiers [7]. The World Health Organization recommends that preterm infants should be fed mother's own milk and donor human milk when a mother's own breast milk is not feasible. Furthermore, the guidelines emphasize that HMFs must be preferably HMDF [21].

The study has certain limitations. It was a single-center descriptive cohort study; hence, the results may not be amenable to generalization. The sample size of the study was small, and a larger study, which includes a post-discharge follow-up of the infants, is needed to be conducted to reinforce the findings of this study.

CONCLUSION

Our study presents evidence that the new 100% HMDF ensures EHMD and also is a safe option for the growth of VLBW preterm infants. The results indicate good feed tolerance with no clinically significant record of adverse events.

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