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Original paper

Bovine milk-based and human milk-based fortification for postnatal weight gain in very preterm neonates—a cohort study

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ABSTRACT

BACKGROUND AND OBJECTIVES: Postnatal growth failure happens in about half of the very low birth weight infants and this can have long-term consequences. Human milk-based multi-nutrient fortifiers (HMBF) are thought to be better tolerated than bovine milk-based multi-nutrient fortifiers (BMBF), thus facilitating early progression to full feeds and improved growth in preterm neonates. This study was done to find the advantage of HMBF over BMBF on postnatal growth and other clinical outcomes.

METHODS: This is a retrospective cohort study where babies <1500 g birth weight or gestational age <32 weeks were included to compare the velocity of weight gain (g/kg/day), duration of hospital stay and clinical outcomes between fortification using HMBF and BMBF till 34 weeks postmenstrual age.

RESULTS: Eligible neonates included in the study were 322, out of whom 123 (37%) received HMBF and 209 (63%) received BMBF. During the stay, 18 babies were changed from BMBF to HMBF and vice versa in 24 babies due to logistic reasons and parents' preferences. The mean birth weight of the babies was 1124 ± 237 g. Weight gain was higher in the exclusive HMBF group [mean difference 0.77 (0.14, 1.39) g/kg/day; *p*-value = 0.018]. Feed intolerance [odds ratio (OR) 0.45 (0.22, 0.95), *p*-value 0.037] was also significantly less in this group. However, other morbidities did not differ significantly between the groups.

CONCLUSION: Higher weight gain and lower feed intolerance in the HMBF group underscores the possible advantage of using HMBF over BMBF. Larger prospective studies might bring out its effect on the duration of hospital stay and other morbidities.

KEYWORDS: premature, neonate, human milk, fortification, weight gain, feed intolerance

INTRODUCTION

Prematurity is the most common cause of under-five mortality [1]. Preterm infants have increased nutritional demands for both baseline and catch-up growth [2]. Optimal postnatal nutrition decreases the mortality and neuro-morbidity among premature infants [3]. Human milk (HM) alone is not sufficient to meet the increased energy (110–135 kcal/kg/day) and protein (3.5–4.5 g/kg/day) requirements and additional supplementation with multi-nutrient fortifiers along with HM is required [3]. Unfortified milk can also lead to low bone mineral

density and poor postnatal growth [4]. The American Academy of Pediatrics (AAP) recommends fortification of HM as the standard of care in preterm infants, less than 1500 g at birth [5].

Neonates fed on donor human milk had better in-hospital growth than the formula-fed neonates [6]. Thus, it has been postulated that human milk-derived multi-nutrient fortifiers would extend the same benefit as breast milk and thus might improve feed tolerance and growth [6, 7]. This in turn might facilitate progression to full feeds, thereby decreasing the duration of parenteral nutrition and the need for venous access. Hence, the use of human milk-based multi-nutrient fortifiers (HMBF) is proposed as a strategy to decrease morbidity and to improve growth in preterm infant. However, the recent Cochrane review found only one well-performed study with these fortifiers being used in preterm neonates on exclusive breast milk and there was insufficient evidence to conclude on their impact on growth or morbidities [8, 9]. Another meta-analysis showed a low-quality evidence of reduced necrotizing enterocolitis (NEC) and lesser weight gain in preterm neonates receiving HMBF [10]. Some tertiary care neonatal units prefer to practice HMBF [11], while most of the units use bovine milk-based multi-nutrient fortifiers (BMBF) as their routine method of fortification [12]. Hence, to address the paucity of evidence on the effect of this emerging practice, we compared growth in very low birth weight neonates fed with human milk fortified using HMBF and BMBF.

MATERIALS AND METHODS

This was a retrospective cohort study done in level III neonatal intensive care unit after institutional ethics committee approval (IEC-NI/20/June/75/46). We included very low birth weight infants (birth weight <1500 g) and/or preterm neonates born before 32 weeks of gestation, admitted between June 2018 and June 2020 who were on fortified milk feeding for more than 1 week. Neonates with congenital gastrointestinal anomalies, major congenital malformations and chromosomal abnormalities were excluded. Case sheets of eligible neonates were retrieved from the medical records department using the ICD code (P07.3). Baseline characteristics, feeding characteristics, weight gain from the day of fortification till 34 weeks of gestational age among both groups, demographic details such as maternal age, gestational age, birth weight, sex, mode of delivery, maternal comorbidities (pregnancy-induced hypertension, gestational diabetes mellitus and doppler abnormalities) and clinical details like respiratory support at birth, feeding characteristics, duration of total parenteral nutrition (TPN), time taken to reach full feeds, time taken to reach birth weight and clinical outcomes of the baby were collected in a structured proforma. Weight of the infant was measured daily around the same time in the morning using the same weighing machine with an accuracy of ±5 g (calibrated at regular interval). Head circumference of the infant was measured once a week using non-stretchable tape.

Feeding and fortification protocol

Initiation and increment of feeds were done as per unit protocol. All hemodynamically stable neonates were started on trophic feeds on day 1. The initial feeding rate is 20 and 30 ml/kg/day for infants' weighing <1000 and >1000 g, respectively. Increment in feeds was done 30 ml/kg/day for infants weighing <1000 g and 40 ml/kg/day for infants >1000 g. As a unit protocol, only mother's own milk (MOM) or donor human milk is given to very preterm babies. Donor human milk was obtained from human milk bank in the city. Fortification was started when the infant reached day 6 of life and feed volume >100 ml/kg/day. Parents were counselled regarding the available options for fortification (BMBF and HMBF) including their source, composition, duration and cost. Approximately, the cost of HMBF is 10 times that of the BMBF sachet. Based on their choice, the type of fortifier was selected. Fortification was withheld during blood transfusion and during medical treatment of patent ductus arteriosus. Vitamin D supplement was also added by 14 days of life so as to give a total intake of 400 IU of vitamin D/day.

Types of fortifiers used

1) Bovine milk-based fortifiers: the two preparations of BMBF used in our unit were
   a) Lactodex-HMF, 1 g/sachet; Raptakos, Brett & Co. Ltd and
   b) Pre-NAN HMF, 1 g/sachet; Nestle & Co. Ltd.
2) Human milk-based fortifier: used in our unit was Neolact-MMF, 1 g/sachet; Neolacta Lifesciences.

Both are available in powdered form. One gram of fortifier was added to 25 ml of human milk.

Outcomes

Our aim was to compare the velocity of weight gain (g/kg/day), rate of increase in head circumference, duration of hospital stay, comorbidities like feed intolerance, NEC, retinopathy of prematurity (ROP), metabolic

bone disease (MBD), bronchopulmonary dysplasia (BPD) at 36 weeks of post-conceptional age, sepsis and all-cause mortality. Feed intolerance was defined as significant vomiting and/or abdominal distension warranting nil per oral for at least 12 h after excluding other causes including NEC. Modified Bell's criteria by Walsh and Kleigman [13] were used for NEC. Bronchopulmonary dysplasia is defined as need for oxygen at 36 weeks corrected gestational age [14]. The metabolic bone disease was considered when ALP >900 IU/l and phosphorus <5.6 mg/dl or a single value of ALP > 1000 IU/l [15].

Statistical analysis

We used descriptive statistics to describe baseline variables. We compared categorical outcome variables by Chi-square test or Fisher's exact test, normally distributed variables by Student's *t*-test and variables with skewed distribution by Mann–Whitney *U*-test. Individual predictors for mortality were determined by univariate analysis. *P*-value <0.05 was considered statistically significant. We used Statistical Software Package SPSS version 23.0 for analysis.

RESULTS

A total of 332 eligible neonates were enrolled from retrospective data, out of whom 123 neonates received HMBF. Among the 209 neonates who received BMBF, two expired before reaching 34 weeks postmenstrual age (PMA) (Figure 1). Eighteen babies were changed from BMBF to HMBF (total babies on exclusive BMBF were 191) and 24 babies were changed from HMBF to BMBF (total babies on exclusive HMBF were 99) during their course of hospital stay due to logistic reasons and parents' preference.

Baseline characteristics such as maternal age, maternal comorbidities, doppler abnormalities, gestation age, birth weight, intrauterine growth restriction, mode of delivery, mode of respiratory support at birth and need for intubation among the two groups were similar (Table 1). The mean gestational age of the BMBF and HMBF groups was 28.4 ± 1.87 and 28 ± 1.87 weeks, respectively. The mean birth weights in BMBF and HMBF groups were 1137.75 ± 237.14 and 1102.47 ± 234.89 g, respectively. Feeding characteristics like initiation of feeds within 24 h, number of babies on MOM/donor milk, number of babies with fortification started before 1 week, day of reaching full feeds and duration of parenteral nutrition were similar between the groups (Table 2). The mean days for reaching birth weight in the BMBF and HMBF groups were 12.3 ± 3.92 and 11.87 ± 3.94 g, respectively, and were not significantly different {odds ratio (OR) [95% confidence interval (CI) 1.03 (0.97, 1.09); *p*-value = 0.3}. Among the babies who received BMBF and HMBF, 147 (70%) and 86 (70%) babies received donor human milk, respectively, during NICU stay.

Weight gain velocity was significantly higher in exclusive HMBF compared among babies on exclusive BMBF after excluding the cross-over babies (mean difference = 0.77 g/kg/day; CI = 0.14, 1.39; *p*-value = 0.015) (Table 3). Among the clinical outcomes, feed intolerance was significantly more in the exclusive BMBF (20%) group than that in the HMBF (10%) group [OR 0.45 (0.22, 0.95), *p*-value 0.037]. However, other clinical outcomes did not differ (Table 4).

Around 10% of the babies in both groups developed culture-positive sepsis [OR 0.91 (0.41, 2.02), *p*-value 0.815]. Among the 21 culture-positive sepsis in the BMBF group, 8 were *Klebsiella pneumoniae*, 6 were *Acinetobacter baumannii*, 3 *Escherichia coli*, 2 *Candida albicans* and 2 *Enterobacter* species. Among the 10 culture-positive sepsis in the HMBF group, 5 were *K. pneumoniae*, 3 were *A. baumannii*, 1 *E. coli* and *Candida auris* each.

DISCUSSION

Several consensuses such as Milan, European Milk Bank Association, European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), and AAP recommends fortifying human milk (HM) for preterm infants with a birthweight of <1800 g [16]. Cochrane review on multi-nutrient fortification by Brown, *et al.* [17] showed fortification increases in-hospital rates of growth of the preterm neonates in terms of weight, length and head circumference. Suboptimal nutrition in preterm infants leads to extrauterine growth restriction which has a significant impact on long-term neurodevelopmental outcomes [18].

Trials comparing bovine milk-based preterm infant formula and HM found that an exclusive HM diet results in a lower incidence of NEC [19, 20]. A dose-dependent reduction in NEC risk attributed to human milk has been observed in several studies [21]. Human milk-based fortification is thought to offer the same benefit of decreased NEC or feed intolerance. We follow multi-nutrient and standard fortification in our unit. We started using BMBF for neonates <32 weeks of gestation or <1,500 g birth weight from the year 2012 and HMBF since 2018. In the USA, about one in five neonatal units used HMBF as of 2015 [11]. It is sparsely

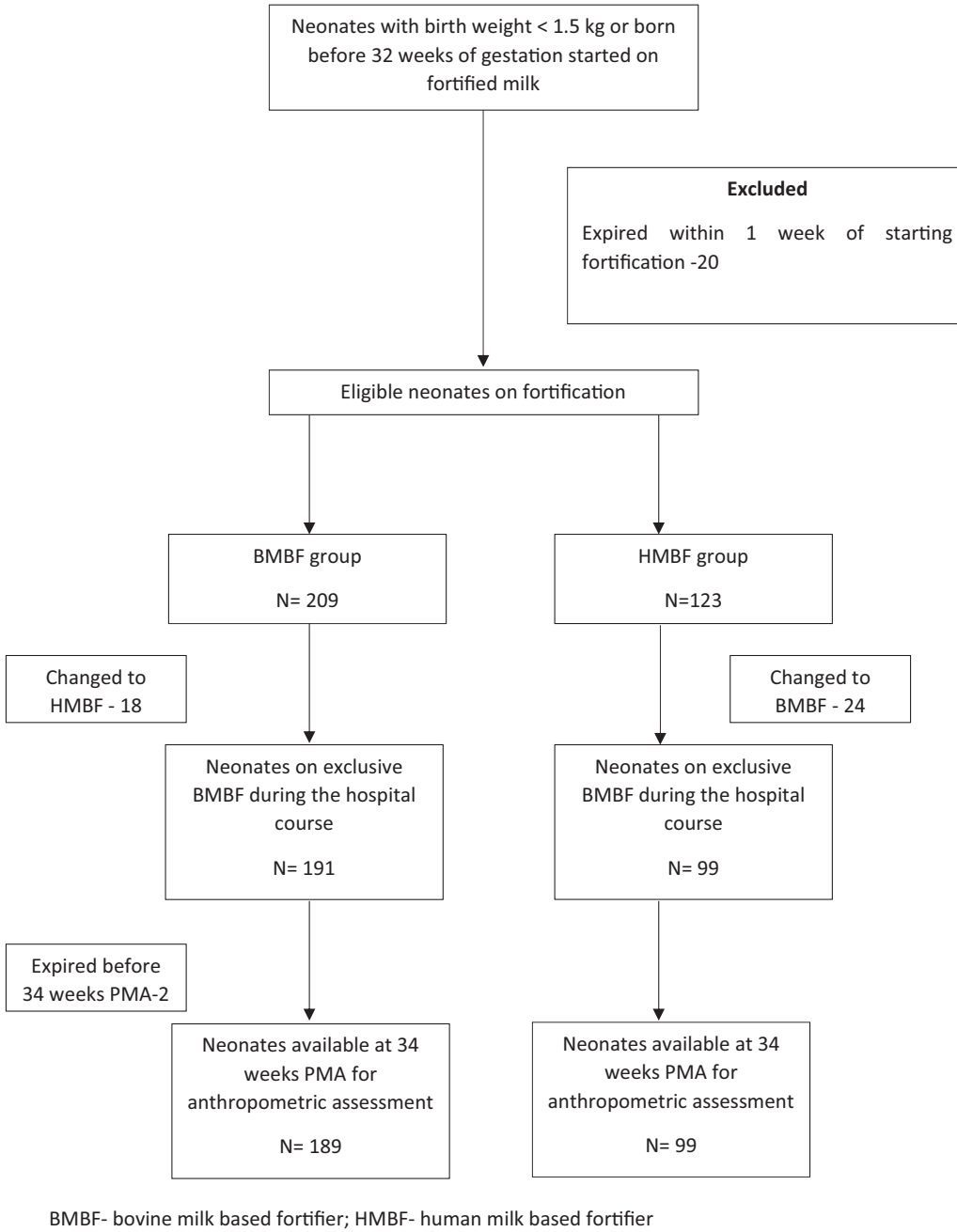

Figure 1. Study flow diagram.

used in developing countries due to the cost involved. In our unit, parents were offered a choice to select any one of the fortifiers after explaining them regarding their nature and the cost involved.

In the study by Sullivan, *et al.* [19], NEC occurrence was significantly lesser in the HMBF group (6%) when compared to the BMBF group (16%). However, in our study, there was no significant difference in NEC occurrence (5% in BMBF vs 2% in HMBF; *p*-value 0.19). In the Sullivan, *et al.* study [19], preterm formula was used in the BMBF group if mother's milk was not available. Hence, many of the babies in the BMBF group who developed NEC were also on bovine formula. The percentage of babies who developed NEC in our study

Table 1. Baseline characteristics of study subjects

Parameters	BMBF ($n = 209$)	HMBF ($n = 123$)
Maternal characteristics		
Mother's age (years), mean± SD	25.8 ± 4.16	25.7 ± 4.19
Pregnancy-induced hypertension	91 (43.5%)	47 (38.2%)
Gestational diabetes mellitus	66 (31.5%)	28 (22.7%)
Doppler abnormalities	67 (32%)	34 (27.6%)
Neonatal characteristics		
Gestational age (weeks), mean± SD	28.4 ± 1.87	28 ± 1.87
Birth weight (g), mean± SD	1137.75 ± 237.14	1102.47 ± 234.89
Male sex	98 (46.8%)	61 (49.5%)
Delivered via caesarean section	88 (42.1%)	64 (52%)
Respiratory support at birth	125 (59.8%)	53 (43%)
Intubation	38 (18.1%)	16 (13%)
CPAP	38 (18.1%)	37 (30%)

All p-values are >0.05. CPAP, continuous positive airway pressure.

Table 2. Feeding characteristics of study subjects

Parameters	BMBF ($n = 209$)	HMBF ($n = 123$)	OR (95% CI)	p-Value
Feeds initiated within 24 h	127 (60.7%)	68 (55.2%)	1.25 (0.79, 1.96)	0.32
Neonate who received mother's own milk/PDHM	192 (91.8%)	114 (92.6%)	0.98 (0.60, 1.59)	0.78
Neonates who received fortification on day 6	200 (96.6%)	116 (94.3%)	1.74 (0.59, 5.08)	0.58
Day of reaching birth weight, mean± SD	12.3 ± 3.92	11.87 ± 3.94	1.03 (0.97, 1.09)	0.33
Day of reaching full feeds, mean± SD	9.49 ± 2.55	9.86 ± 2.55	0.94 (0.86, 1.02)	0.20
Days on parenteral nutrition, mean± SD	5 ± 2.2	5.5 ± 2.8	0.91 (0.83, 1)	0.40

PDHM, pasteurized donor human milk.

(4%) was lower than that in the other study (16%) probably due to exclusive human milk usage either MOM or donor human milk and standardized feeding protocol in our setup. Also, the newer BMBFs have lesser osmolality and enhanced essential fatty acid and protein content compared to older BMBFs [22]. Thus, the newer BMBFs may help in achieving optimal growth without increasing the risk of NEC in preterm infants.

In the meta-analysis by Ananthan, *et al.* [10] which included six RCTs, the HMBF group had significantly lower weight gain than in the BMBF group with significant reduction in risk of NEC ≥ stage II in the HMBF group. However, the studies included in this meta-analysis had lot of heterogeneity in terms of time of commencement, duration of fortification and type of milk. The higher weight gain can be attributed to the nutrient-enriched preterm formula that were used rather than term formula [6]. The OptiMoM study, the first trial comparing the efficacy of HMBF and BMBF in neonates on exclusive human milk in the absence of formula, concluded that there was no difference in feeding tolerance, postnatal increase in length or head circumference and morbidity, including NEC ≥ grade 2 [9]. In Cochrane systematic review which only included the study with preterm neonates on exclusive HM diet, there was no statistical difference in weight gain among the two groups [8]. In our study, all the neonates were on exclusive human milk, either MOM or donor milk and the weight gain was marginally higher in babies on exclusive HMBF group. This might be secondary to decreased feed intolerance and feed interruption in the HMBF group. HMBF has been adopted in some units despite its higher cost probably due to its indirect reduction of costs involved in hospital care by reducing major morbidity like NEC [19, 20].

Fortification not only provides protein but also essential nutrients like calcium and phosphorus. Hagelberg, *et al.* [23] reported serum calcium and phosphorus levels before and after 3 weeks' supplementation with the study fortifiers and found no difference between the groups. Even in our study, there was no difference between the groups. ROP development also could be related to postnatal weight gain. Since poor weight gain increases the risk of ROP as concluded by the WINROP study [24], better postnatal weight could

Table 3. Weight gain velocity and increase in head circumference from initiating fortification till 34 weeks PMA

Growth parameters	BMBF ($N = 207$)	HMBF ($N = 123$)	Mean diff (95% CI)	*p*-Value
Weight gain, mean ± SD (g/kg/day)	12.69 ± 2.41	13.14 ± 2.75	−0.45 (−1.02, 0.12)	0.124
Rate of increase in HC (cm/week)	0.49 ± 0.05	0.49 ± 0.05	0.0003 (−0.011, 0.012)	0.950
	BMBF ($N = 138$)	**HMBF ($N = 74$)**		
Gestation age <30 weeks				
Weight gain, mean ± SD (g/kg/day)	12.53 ± 2.44	12.97 ± 2.66	−0.43 (−1.15, 0.27)	0.228
Rate of increase in HC (cm/week)	0.49 ± 0.047	0.49 ± 0.052	−0.0006 (−0.014, 0.013)	0.928
	BMBF ($N = 69$)	HMBF ($N = 49$)		
Gestation age >30 weeks				
Weight gain, mean ± SD (g/kg/day)	13.02 ± 2.34	13.4 ± 2.88	−0.37 (−1.33, 0.57)	0.436
Rate of increase in HC (cm/week)	0.49 ± 0.06	0.49 ± 0.05	0.002 (−0.194, 0.024)	0.808
	Exclusive BMBF ($N = 189$)	**Exclusive HMBF ($N = 99$)**		
Weight gain, mean ± SD (g/kg/day)	12.68 ± 2.42	13.45 ± 2.87	−0.762 (−1.39, −0.13)	**0.0182***
Rate of increase in HC (cm/week)	0.4915 ± 0.0537	0.4916 ± 0.0539	−0.00002 (−0.013, 0.013)	0.9966

HC, head circumference.
* Any *p*-value <0.05 was taken as significant.

Table 4. Clinical outcomes

Parameters	Exclusive BMBF ($N = 191$)	Exclusive HMBF ($N = 99$)	OR (95% CI)	*p*-Value#
Feed intolerance	38 (20%)	10 (10%)	0.45 (0.22, 0.95)	**0.037***
NEC stage II/III	10 (5.2%)	2 (2%)	0.37 (0.08, 1.74)	0.209
BPD	9 (4.8%)	5 (5%)	1.08 (0.35, 3.3)	0.899
MBD	8 (4.1%)	0 (0%)	0.11 (0.01, 1.9)	0.128
ROP	21 (11%)	10 (10%)	0.91 (0.41, 2.02)	0.815
Duration of hospital stay (days), mean ± SD	23 ± 9	21 ± 9	0.97 (0.95, 1.00)	0.097
Culture proven sepsis	21 (11%)	10 (10%)	0.91 (0.41, 2.02)	0.815
All-cause mortality	2 (0.9%)	0 (0%)	0.38 (0.18, 8.01)	0.535

* Any *p*-value <0.05 was taken as significant was represented in bold.
# Logistic regression.

lead to a decrease in ROP. However, there was no significant difference in ROP incidence.

Human milk has been found to be protective against nosocomial sepsis due to its anti-infective properties [25]. Hence, human milk-based fortification might increase this protective effect. In the study by Jason [26], 90% of young infants with *Cronobacter* sepsis were exposed to powdered infant formula or BMBF. There was no outbreak or difference in the rate of nosocomial sepsis between the two groups and the organisms grown in our cohort was similar to our usual unit pattern.

Strengths of our study are: first study from developing country with large sample size and done with standard feeding protocol with predominant human milk feeding. Limitations are: the retrospective study design, lack of accounting for protein and calorie difference,

feed volume and cost-effectiveness of the fortifier was not studied.

CONCLUSION

Though no difference has been found in the major morbidities between the two groups, there might be a potential advantage of using HMBF over BMBF in exclusively human milk-fed preterm neonates because of the higher weight gain and lower feed intolerance with HMBF. Larger prospective studies might bring out its effect on duration of hospital stay and other morbidities. Assessment of long-term outcomes (bone mineralization and neurodevelopment) and cost-effectiveness also need to be addressed by future trials.

CONTRIBUTIONS

Conception/design of the research, U.D. and P.A.; acquisition, analysis or interpretation of the data, R.S., U.D. and U.B.; initial draft of the manuscript, R.S. and U.D.; critical revision of the manuscript, P.A. and U.B.; and supervision, P.A. and U.D. All authors read and approved the final article.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author, U.D., upon reasonable request.

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