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Original Research Article

EFFECT OF FORTIFICATION OF HUMAN MILK WITH HMF VERSUS INFANT FORMULA POWDER ON THE GROWTH OF VLBW BABIES

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Abstract

Background: It is observed that human milk fed preterm babies has slower growth rate & inadequate specific nutrient intake to fulfill their greater needs. Fortification of human milk increases short term weight gain & length in preterm VLBW babies however the high cost & Increase risk of feed intolerance limit their widespread use. Preterm formula powder might be more cost effective alternative for fortification of human milk in resource constrained setting like India.The objective is to compare the effect of fortification of human milk with HMF & preterm formula milk on growth parameters of VLBW neonates. **Materials and Methods:** All babies less than 34 weeks and 1500gms born during study period Nov. 2018 to Dec. 2019, born at Maharaja Agrasen hospital New Delhi were included in the study. Neonates were randomly assigned to receive fortification by either HMF or preterm formula once the babies reached full feeding volumes (150 ml/kg/day). **Result:** A total of 121 neonates were assessed for eligibility, out of which 40 were excluded. Of the 81 neonates enrolled 41 & 40 were randomized to the HMF & PTF (preterm formula) group. Six & 4 Neonates were excluded from HMF & PTF group respectively due to lost to follow up. A total of 71 babies (35 in HMF & 36 in PTF) were available for analysis. The mean gestation (29.97 Vs 29.99 weeks) & birth weight (1248 Vs 1251grms) were comparable between the groups. There was no difference in the mean (SD) Weight gain between the HMF & PTF groups (17.83[2.28] Vs 18.04 [1.99] gm/kg/day). There was no different in the mean (SD) linear growth (1.07 [14] Vs 1.07[0.12] cm/ week). Head circumference growth were also similar in both group (0.97[0.13] Vs 1.0 [0.14] cm/ week). The incidence of feed intolerance was more common in the group fortification with HMF. This was not statistically significant. There was one case of NEC in the fortification with PTF group which was excluded from the trial as per study protocol. **Conclusion:** Growth pattern of VLBW babies fed on milk fortified either with HMF or preterm formula is very similar. Given the similar incidence of feed intolerance and lower cost, Preterm formula might be a better alternative for fortification, especially in recourse restricted setting.

INTRODUCTION

Human milk is considered the best source of nutrition for all preterm newborn babies due to several nutritional and immunological advantages.[1-9] VLBW premature babies exclusively fed on human milk during hospitalization fail to show growth rates comparable to intrauterine growth rates due to inadequate protein and minerals in expressed human milk for growing premature babies.[10-13] Growth failure in preterm VLBW babies has been attributed due to protein deficiency rather than energy deficit.[14-16] There is physiological decline in concentration of protein, sodium, zinc and other micronutrients throughout lactation which leads to inadequate nutrient supply and finally growth failure in preterm infant.[17] To meet the need of higher protein, calories and minerals, fortification of human milk has been recommended as the standard of care.[1] The only easily available human milk fortifier in India is lactodex HMF. Another HMF 'Nestle Pre NAN HMF' has becomerecently into the market. There are several limitations with the use of lactodex HMF.[18] This includes added daily cost (200 rs/day) and lack of Iron and poor availability in smaller cities

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&town.[19-21] There are very few studies showing improved weight gain pattern, linear growth and head circumference growth in fortified group using lactodex HMF. Unlike HMF, Infant milk powder is freely available and is cheaper alternative. The addition of infant formula powder to human milk increase protein content of preterm human milk to 2.0-2.9 gm/100 ml.[17] In view of significant limitations of the available HMF and very few reports in literature of use of term/preterm infant formula for human milk fortification,[18,21,22] we compare the effect of fortification of human milk with HMF Vs infant formula powder on the growth of VLBW babies.

Objective

To evaluate differences in weight gain, linear growth and head circumference of VLBW babies feeding on expressed breast milk fortified with HMF and with infant formula powder.

MATERIALS AND METHODS

It was prospective, open, parallel group randomized control trial conducted at tertiary care neonatal unit. All babies <34 weeks with <1500 gm born during the study period (Nov. 2018 to Dec. 2019) born as Maharaja Agrasen hospital, New Delhi were included in the study. The babies were randomized in two groups (fortified human milk with HMF or fortified human milk with infant formula powder). Once the babies reached full feeding volumes (150ml/kg/day) statistician involved in the study generated the random allocation sequence and serially numbered opaque sealed envelopes were used to conceal the allocation. Fortification of human milk was done using HMF sachet (lactodex-HMF, Raptakos) and an infant formula powder (pre NAN Nestle). Each 25 ml of expressed breast milk was fortified with 1 gm sachet of HMF (Group A) or with addition of 1 gm infant milk formula powder (Group B). Final osmolality of fortified milk was measured using freezing point depression. Osmometer

The primary outcome measured was weight gain in g/kg/day in 2 groups from the dates of randomization until the baby reached 1800gm. The secondary outcome measured were linear growth [Length gain in cm/week, calculated as (length on the end point – length on the day of recruitment) x 7/ number of days baby was in study], head circumference increase (Head circumference gain in cm/week) calculated as [(head circumference on the end point – head circumference on the day of recruitment) x7/ number of days baby was in study], duration of hospital stay and co morbidities like feed intolerance, sepsis and necrotizing enterocolitis between the groups.

RESULTS

A total of 121 neonates were assessed for eligibility, out of which 40 were excluded. Out of the 81 neonates enrolled 41 and 40 were randomized to the HMF and preterm formula groups. Six and 4 neonates were excluded from HMF and PTF group respectively due to lost to fallow up. [In HMF group – withdrawal of consent-2, LAMA-3, hydrocephalus-1, In PTF group – LAMA-3, NEC-1]

A total of 71 babies (35 in HMF and 36 in PTF) were available for analysis. Statistical tests were applied as follow (1) Quantitative variable were compared using t test/Mann-Whitney test (when the data sets were not normally distributed) between the 2 groups, (2) Qualitative variable were corrected using Chi square test/Fisher's exact test. A p value of <0.05 was considered statistically significant.

Baseline neonatal demographic variable:

All baseline neonatal demographicvariables were comparable between the 2 groups.

Table 1: Base line neonatal demographic variables

	Group A (n=35)	**Group B (n=36)**	
Variable	Mean ± SD	Mean ±SD	P value
Gestational age	29.97±1.32	29.±1.3	0.872
Male* Female*	13(37.14) 22(62.86)	15(41.67) 21(58.33)	0.88
Birth weight (g)	1248.66±133.17	1251.33±131.54	0.868
Head circumference at birth (cm)	27.74+1.42	27.7±1.49	0.715
Length at birth (cm)	38.1+2.0	38.2+2.1	0.94
Weight at recruitment (g)	1180.8±190.5	1175.8+166.0	0.86
Head circumference at recruitment (cm)	27.3±1.4	27.3±1.2	0.72
Length at recruitment (cm)	40.12±2.26	40.22±2.48	0.468
Day of recruitment	13.11±3.25	12.86±3.51	0.75

Outcome variables

All primary outcome variables are comparable between the two groups. The weight gain velocity (gm/kg/day) was 17.83 ±2.28 in group A and 18.0±1.99 in group B. The difference in weight gain velocity was not significant statistically (p value -0.658). The overall linear growth (length gain in cm /week 1.07±0.14 cm in group A and 1.07±0.12 cm in group B, p=0.535) was similar in both groups (Table 2). The head circumference growth in group B was greater than group A, though it was statistically not significant (head circumference gain in cm/ week (0.97±0.13 cm vs 1.0±0.12 cm: p= 0.309).

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Table 2: Outcome variables: Anthropometric variables between the two groups

	Group A (N=35	Group B (N=36)	
Variable	Mean ±SD	Mean ±SD	P value
Weight gain (g/kg/day)	17.83±2.28	18.04±1.99	0.65
Linear growth (cm/week	1.07±0.14	1.07±0.12	0.535
Head circumferencegrowth (cm/week)	0.97±0.13	1.0±0.14	0.30

Table 3: Comparison of preterm human milk on day 7 and day 28 of lactation.[17]

	Preterm HM (1 week)/ 100ml	Preterm HM (1 month)/ 100ml
Energy (Kcal)	67	69
Protein (g)	2.4	1.5
Fat (g)	3.8	3.6
Carbohydrate (g)	6.1	6.7
Calcium (mg)	25	29
Phosporus (mg)	14	9.3
Zinc (µg)	500	215
Vitamin A (IU)	560	227
Vitamin D (IU)	4	1.2

Presently for optimal growth in of preterm VLBW babies, higher protein intake (range 3.5 to 4.5 gm/kg/ day) with adequate calories maintaining normal Protein/Energy ratio is recommended.

Table 4: Nutritional Recommendations for preterm VLBW baby

	ESPGHAN,[28]	Canadian pediatric society,[27]	AAP committee on nutrition,[29]	LSRO,[26]
Energy(kcal/kg/day)	110 -135	105 - 135	105 - 130	110-135
Protein(g/kg/day)	3.5 – 4.5(4-4.5)*	3 – 4(3.5 – 4)*	3.5 – 4.0	3.4-4.3
Protein/Energy (g/ 100 kcal)	2.25 – 3.1	2.5 – 3.0	2.9 – 3.3	2.5.-3.6

*ELBW Babies

Table 5: Nutrient composition of Preterm Human Milk and variousfortifying options availableinIndia.[17,19,30]

Nutrition	Preterm Human Milk	Infant Milk Formula(Pre Nan) used	Lactodex HMF	Nestle HMF
Calories (Kcal)	69	3.0	3.7	4.3
Protein(g)	1.5	0.117	0.1	0.36
Fat(g)	3.6	0.24	0.05	0.18
Calcium(mg)	29	6.10	25	18.90
Phosphorus (mg)	9.3	3.05	12.5	10.95
Iron (mg)	0.12	0.09	-	0.45
Vitamin A (IU)	227	59	60	277
Vitamin D (IU)	1.2	25	19	35

DISCUSSION

Preterm VLBW babies require higher protein, minerals and vitamins for achieving adequate growth velocity and feeding exclusive on human milk may not be sufficient. This leads topost-natal growth failure. Atkins etal,[10] showed that VLBW babies fed their own mother milk do not have adequate calcium and phosphorus intake. This growth failure associated with un-supplemented human milk has been attributed mainly due to protein deficiency rather than total calories. Protein plays an important role in optimal neurodevelopment as it may be required for normal process of neurogenesis, dendritic arborization, synaptogenesis, myelination and cell signaling via growth factors and neurotransmitters.[23] Hence inadequate protein intake is a limiting factor for growth and neurocognitive development.[24-26]With increase duration of lactation there has been physiologic decline in concentration of protein and other nutrient like sodium, zinc in breast milk.[17]

The easily available milk fortifier in India is lactodex HMF and more recently Pre NAN HMF. HMF is not easily available in small town and cities. Fortifications of human milk with lactodex HMF cost Rs. 180-220/ day. Poor availability and higher cost are the main limitations for the use of HMF. Many people still do not advocate the routine use of fortifier and reserve its use in case of growths faltering in preterm (<32wk) VLBW babies in India.[30]

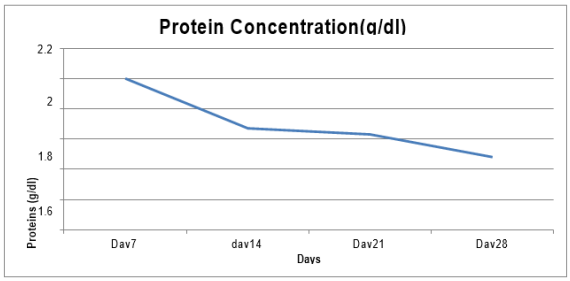

Figure 1: Protein concentration of Preterm human milk at different stages of lactation

To overcome the limitations of the HMF, there are some reports of infant milk powder being used for the fortification of preterm human milk. Several suggested using preterm infant formula for

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fortification of human milk when HMF can't be used because of unavailability or cost factor. Sankar et al,[21] from India suggested using preterm infant formulafor fortification of human milk when HMF can't be used because of unavailability or cost factor.Khorana et al,[31] conducted a pilot study from Thailand comparing the post- discharge milk powder formula used as a fortifying agent with HMF for preterm human milk fortification. They did not find any significant differences in terms of growth parameters, biochemical parameters, duration of stay, morbidities (definite NEC and osteopenia of prematurity) between the two groups.

Comparison of Growth Parameters

The use of HMF and infant milk powder for fortification of preterm human milk in our study resulted in almost similar weight gain rate in two groups (17.83 ± 2. g/kg/day vs. 18.0 ±1.99 g/kg/day; p = < 0.65). Linear growth rate and head growth circumference were also not significantly different between two groups (1.07±0.14 cm/week vs. 1.07±012 cm/week p=0.535) and (0.97±0.13 cm vs. 1.0±0.12 cm: p= 0.309) respectively.

The growth rate after fortification with HMF and infant formula powder in our study was more or less comparable to pilot study done by Khorana et al,[31] compared the fortification of human milk with HMF vs. post discharge formula, where they found no difference in the growth parameters between the two suggesting non inferiority, when using post discharge formula for human milk fortification in low resource settings.

Kumar et al,[32] demonstrated beneficial effect of protein supplementation on growth of preterm VLBW babies. The use of lyophilized human milk protein or casein hydrolysate resulted in average increase in weight gain of 3.6 g/kg/day, increase in length of 0.28cm /week (weighted mean difference) and head circumference growth difference of 0.15 cm/week (weighted mean difference). As growing preterm babies do require extra calcium, phosphorus, minerals and vitamins along with proteins when on exclusive breast milk, this strategy gave way for multi- component fortification. Though most studies done across the world showed definite advantage of multi- component fortification, there is wide heterogeneity among the different fortifiers available and the strategies for milk fortifications. In India however, not many options are available, so infant formula powder can be used as human milk fortifier.

Arslanoglu et al,[33] showed significantly improved weight gain (18 g/kg/d vs. 14 g/kg/d, p= <0.01) and head growth (1.0 cm/week vs. 0.7 cm/week; P<0.05) by using adjustable fortification as compared to standard fortification of human milk. The anthropometric parameters attained by adjustable fortification were almost similar to what we attained in our study (18.0 ±1.99g/kg/day).Increased osmolality of fortified human milk has raised the concern offeed intolerance and NEC. The addition of infant milk powder increases the osmolality from the baseline of 303miliosmol/kg to 397miliosmol/kg in our study. The difference between the rate of feed intolerance was not statistically significant in both groups (6 [17.17%] Vs 5 [13.80], p= 0.75).

Lukas et al ((34) reported incidence of NEC in fortified group (5.8% Vs 2.2%, p= 0.12) through there was significant use of preterm formula in both groups. A Cochrane review in 2004 (including 7 trials & 640 infants to look for NEC as outcome) refuted the claim of increased incidence of NEC in fortified human milk when compared to unfortified human milk in preterm infants (RR-1.33, 95% CI 0.7-2.5). In our study there was only one case of NEC in the fortification with infant formula powder group, which was excluded from the analysis as per study protocol.

CONCLUSION

Preterm VLBW babies fed exclusively human milk fail to grow at rates comparable to intrauterine growth rates. Postnatal growth failure has been shown to increase the risk of long term poor neurodevelopmental and neurocognitive outcome. Fortification of human milk to provide optimum nutrition to growing preterm babies is the standard of care across the world. Fortification of human milk in developing countries like India is still a challenge in view of the use of infant milk powder limited availability and cost. The use of infant milk powder for human milk fortification showed significant similarity in the weight gain velocity, linear growth and head growth rate in preterm VLBW babies when compared with using HMF fortified human milk. Similarly, there is no adverse effect or difference in the co morbidities. The use of infant milk powder as human milk fortifier is a practical, feasible, and cheaper alternative for improving growth of VLBW babies in middle income countries like India.

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