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Feed fortification for enteral nutrition in low birth weight infants-LBW Formula vs HMF- An RCT

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Abstract

Introduction: Premature delivery and intrauterine growth restriction results in decreased nutrition deposition in infant. Fortification of expressed breast milk with Human Milk Fortifier (HMF) or Low Birth Weight(LBW) powder increases the nutrient content of milk without compromising its other beneficial effects.

Materials and Method: A randomized control study was undertaken to compare efficacy of the fortification of HMF vs LBW formula in breast milk feeds of babies who were hospitalized and weighed less than 2kg. The time to regain birth weight was considered the primary outcome. Secondary outcomes analysed were feed intolerance as evidenced by increased pre-feed residues, vomiting, abdominal distension and NEC.

Results: Total 96 babies were included in the study(46 HMF group & 46 LBW group). The time to regain birth weight was 6.09+/- 1.834 in HMF group and 7.32+/-2.69 in LBW group(p=0.39) which was comparable between the two groups except in the term babies in the HMF group who regained birth weight significantly faster than the LBW formula group**(p=0.05)**. The secondary outcomes of feed intolerance viz. prefeed residue, abdominal distension and necrotizing enterocolitis occurred more frequently in LBW group as compared to HMF group, but the result was statistically not significant. However, incidence of vomiting was significantly more in LBW group**(p=0.03)**. The average cost of fortification per patient was more in HMF group(262 INR) as compared to LBW group(10.2 INR) and the difference was highly statistically significant **(p<0.0001).**

Conclusion: The fortification of breast milk with human milk fortifier is as efficacious as low birth weight formula. Both the fortificants were equally well tolerated except for vomiting which occurred more with LBW formula fortification. The cost of treatment with LBW formula fortification was considerably cheaper than the HMF group. We therefore recommend LBW formula fortification of breast milk in low birth weight infants for quicker weight gain in the low resource setting.

Keywords: Fortification, Low Birth Weight Powder, Human Milk Fortifier

Introduction

Globally, about 18 million infants are born with a birth weight of <2500g every year.(1) Though these low birth weight (LBW) infants constitute only about 14% of the total live births, they account for 60-80% of total neonatal deaths.(2) Most of these deaths can be prevented with extra attention to warmth, prevention of infections and more importantly, optimal feeding.

Providing optimal enteral nutrition to high-risk premature neonates is a difficult clinical challenge. Premature delivery and intra uterine growth restriction results in decreased nutrient deposition in the infant. Critical illness and prolonged respiratory support delays initiation of enteral feeding in extreme premature and very low birth weight infants. Immature gut motility and function often preclude intended delivery of nutrition. Risk of necrotizing enterocolitis if feeds are advanced too quickly may also limit provision of optimal enteral nutrition. Consequently, the premature infant requires specialized nutritional support to meet these great demands for growth in addition the nutrient reserves are limited due to premature birth.

When fetal life is interrupted by premature birth, significant protein and weight deficits can occur.(3) These babies have increased nutritional requirements due to rapid growth as well as the stress factor of several morbidities that a premature birth is accompanied by. Thus, achieving optimal postnatal growth in this subset of population is difficult. Hence nutritional support in these babies achieves vital importance.Increased nutritional demands of the preterm and LBW infants needs to be met with both increased calories as well as proteins.

Breast milk has inadequate amounts of protein, energy, calcium, phosphorus, trace elements(iron, zinc) and vitamins (D, E & K) that are unable to meet the increased demands of these infants. Hence their daily recommended intakes need multi-nutrient supplementation till they reach term gestation (40 weeks postmenstrual age).[4]Fortification of expressed breast milk with HMF or LBW powder increases the nutrient content of the milk without compromising its other beneficial effects e.g. reduction of NEC, infections, etc. The Cochrane review on fortification found short term improvement in weight gain, linear and head growth without any increase in adverse effects such as NEC.(5,6)

This study was undertaken to compare the nutrition accretion rate as evidenced by time to regain birth weight as well as occurrence of feed intolerance viz. prefeed residue, vomiting, abdominal distension, NEC) in infants with birth weight < 2000 gm upon fortification of expressed breast milk with low birth weight formula powder vs human milk fortifier.

Aims and Objectives

This study aimed at comparing the nutrition accretion rate in preterm infants who received fortification of expressed breast milk with HMF vs LBW formula, as evidenced by time to regain birth weight and the side effect profile as studied by prefeed residue, vomiting, abdominal distension and necrotizing enterocolitis. The hypothesis was that fortification of expressed human milk with low birth weight milk powder is equally efficacious and a cheaper alternative to human milk fortifier in achieving effective weight gain in preterm infants.

Materials and Method

This randomized control study was conducted in Neonatal Intensive Care Unit at a tertiary care hospital between February 2016 to January 2017. Parental consent was obtained prior to enrolment in the study. Sanction of the institutional ethical committee and hospital research committee was obtained. The study population comprised of all babies hospitalized in the NICU with birth weight of less than 2000 gm who have reached full enteral feeds and mother's expressed breast milk was available. The neonates with non availability of mother's milk, birth weight more than 2 kg, babies on parenteral nutrition or major congenital anomaly were excluded from the study. A statistically significant sample size was calculated to be 92.

The neonates were assigned to HMF and LBW group as per computer generated randomization tables. Mother's milk was expressed by mechanical or electronic breast pump under sterile conditions and was kept in refrigerator at 4 degree centigrade and pre-warmed to room temperature before administration to her baby. Minimal enteral feeds were started at the earliest and advanced as per tolerance. On reaching full enteral feeds, Simyl MCT oil was added (0.5ml alternate feeds) and was increased by 0.5ml all feeds followed by 1ml all feeds as per tolerability and weight gain/day. A day after full enteral feeds was reached EBM was fortified with human milk fortifier(1g/25ml) or low birth weight formula(1g/25ml) to all feeds. Total calories, protein and Non-Protein Calorie/Nitrogen ratio was recorded for each baby.Neonates were weighed daily on an electronic weighing scale and weight gain was recorded. Time taken to regain birth weight was recorded. Feed intolerance as evidenced by pre-feed residue, vomiting, abdominal distension and necrotizing enterocolitis was recorded if it occurred.

The data was recorded and entered into Microsoft Excel Spreadsheet. Statistical analysis was done using unpaired t-test, Fischer exact and chi square test.

Results and Analysis

Incidence: During the study period, there were a total of 831 admissions in the NICU. Of these 187 neonates had a birth weight of < 2kg. Those who met the inclusion criteria and completed the study constituted 49% (92 babies) of the low birth weight formula group(< 2kg).

Gestational Age-Wise Distribution: Of the 92 babies enrolled in the study, 10 babies(HMF-6, LBW-4) were <28 weeks, 22 babies(HMF-10, LBW-12) were between 28 to 31 weeks, 46 babies (HMF-22, LBW-24) were between 32 to 34 weeks, 6(HMF-4, LBW-2) babies were between 35 to 37 weeks and 8 babies(HMF-4, LBW-4) were above 37 weeks.

The distribution between the two groups across all gestation age groups was comparable as shown in Fig. 1.

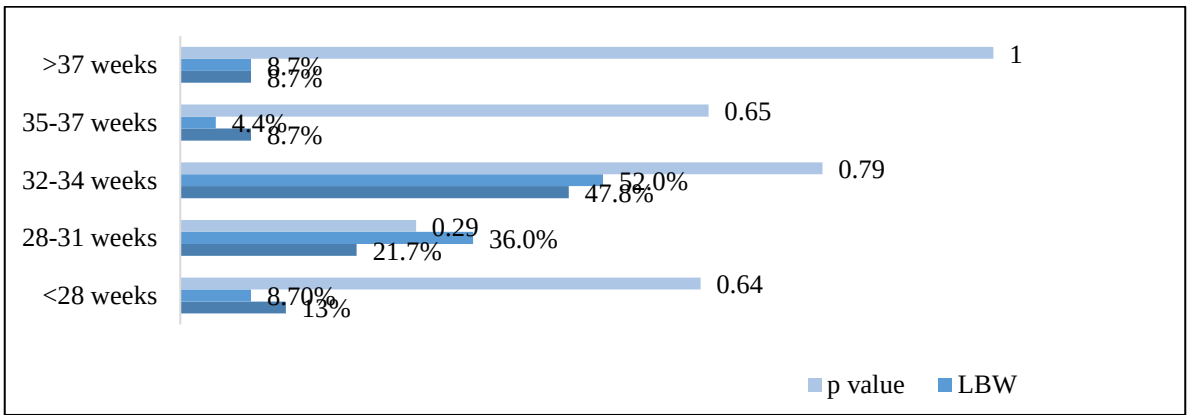

Fig. 1: Gestational age-wise distribution

Birth Weight-Wise Distribution: Of the 92 babies included in the study, 10 babies were below 1 kg birth weight(HMF-6, LBW-4), 42 babies were between 1000 to 1500g (HMF-20, LBW-22), and 40 babies were between 1500 to 2000 g(HMF-20, LBW-20). The distribution between the two groups across all birth weight groups was comparable as shown in Fig. 2.

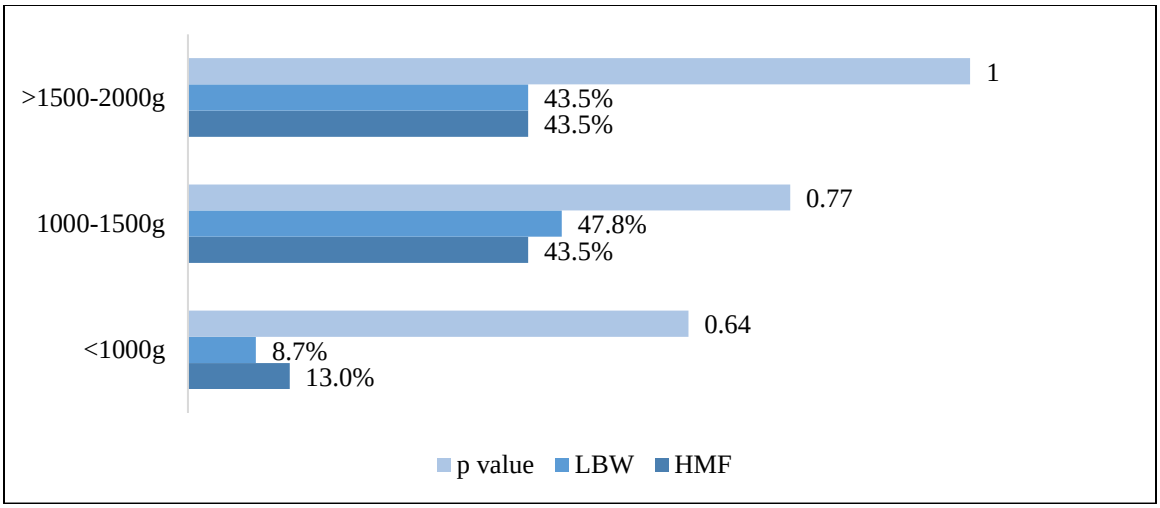

Fig. 2: Birth weight-wise distribution

Gender Distribution: In our study of 92 babies, 66 were males (HMF-32, LBW-34) and 26 were females (HMF-14, LBW-12)[p=0.74].

Age to Reach Full Enteral Feeds: Full enteral feeds was reached by 8 babies(HMF-4, LBW-4) between 1st to 4th day of life, 42 babies (HMF-22, LBW-20) between 5th to 7th day of life.22 babies(HMF-10, LBW-12) between 8th to 10th day of life, 14 babies(HMF-6, LBW-8) between 11th to 15th day of life and 6 babies(HMF-4, LBW-2) more than 15th day of life as shown in Table 1.

Table 1: Age at full enteral feeds

DOL	HMF		LBW		p value
	N	Percentage (%)	N	Percentage (%)	
1-4	4	8.7	4	8.7	1.00
>4-7	22	47.8	20	43.5	0.77
>7-10	10	21.7	12	26	0.73
>10-15	6	13	8	17.4	0.68
>15	4	8.7	2	4.4	0.56
Total	46		46		

It was observed that in both study groups, the time taken to reach full enteral feeds was comparable with no statistically significant difference observed.

Time to Regain Birth Weight

a. It was seen in the study that in the HMF group the babies regained birth weight in a mean of 6.09+/-1.834 days and in LBW formula group in 7.32+/-2.69 days. This increased time taken in the LBW formula group when compared with HMF group did not reach levels of statistical significance (p=0.39). However, term babies in HMF group regained birth weight earlier as compared to LBW formula and the result reached levels of statistically significance **(p=0.05)** as shown in Table 2.

Table 2: Time to regain birth weight vs Gestation age

Gestational Age (weeks)	HMF(days)	LBW(days)	P value
<28	4.25+/-1.89	4.5+/-3.54	0.915
28-31	8+/-1.41	7.67+/-3.51	0.33
32-34	7.2+/-1.98	5.6+/-3.74	0.3
35-37	7+/-0.71	8+/-0.71	0.29
>37	4+/-0.71	7+/-0.71	0.05

b. Average Daily Weight Gain: The average daily weight gain in both study groups which are HMF vs LBW formula supplementation was further analyzed. It was seen that average weight gain in extreme preterms was 18g/kg/d in HMF and 21g/kg/d in LBW formula group, in the early preterms 13g/kg/d in HMF and 13g/kg/d in LBW formula group, in preterms was12g/kg/d in HMF and 11g/kg/d in LBW formula group whereas it was 12g/kg/d in HMF and 8g/kg/d in LBW group in late preterms and 10g/kg/d in HMF and 7g/kg/d in LBW formula group in term babies as shown in Table 3.

Table 3: Weight Gain (g/kg/d)

Gestation age(weeks)	HMF	LBW	P value
<28	18+/-2.65	21+/-2.12	0.14
>28-31	13+/-5.2	13+/-5.06	1
32-34	12+/-5.3	11+/-8.6	0.69
35-37	12+/-0.71	8+/-0.71	0.051
>37	10+/-0.71	7+/-0.71	0.051

The average daily weight gain in extreme preterms, early preterms and preterms were comparable between the two groups and the result was statistically not significant. However, the average daily weight gain among late preterms and term babies was more in HMF group as compared to LBW formula supplementation

and almost reached levels of statistical significance(p=0.051).

Mean Calories & Proteins Provided: The mean calories provided for all babies was calculated and the mean calorie intake was compared between the HMF vs LBW formula supplementation. It was seen that in HMF group the mean calories was 285.5kcal and 292.1kcal in LBW group(p=0.87). The average proteins provided in HMF group is 4.78 as against 4.17 in LBW milk formula group(p=0.54). The mean calories and mean proteins provided were comparable between the two study groups.

Mean Non-Protein Calorie/Nitrogen: The mean NPC/N was 335.6 in HMF and 366.2 in LBW group. The mean NPC/N was further analyzed between the two groups with reference to gestation age. The mean NPC/N provided in less than 28 weeks was 341.5 in HMF and 390 in LBW formula group, 28 to 31 weeks was 352.4 in HMF and 404.4 in LBW formula group, 32 to 34 weeks was 329 in HMF and 360 in LBW formula group whereas in 35 to 37 week gestation 310 in HMF and 338.5 in LBW formula group while in babies above 37 weeks gestation 345 was provided in HMF and 338.5 in LBW formula group as shown in Table 4.

Table 4: Mean NPC/N vs Gestation age

Gestation Age(weeks)	HMF	LBW	p value
<28	341.5+/-71.4	390+/-70.7	0.56
28-31	352.4+/-35.5	404.4+/-50.3	0.051
32-34	329+/-10.4	360+/-22.3	0.0018
35-37	310+/-1.4	338.5+/-24.7	0.25
>37	345+/-7	338.5+/-24.7	0.75

It was however observed that the average NPC/N was comparable in extreme preterms, early preterms, late preterms and term babies and the result was statistically not significant. However the NPC/N profile was more favourable in the HMF group in classical pre term babies and the result was statistically significant(p=0.0018).

Feed Intolerance-HMF vs LBW Formula Group: The secondary outcomes were studied in the form of intolerance to the supplementation provided as evidenced by side effects viz. pre-feed residue, vomiting, abdominal distension and NEC. The side effects observed between the HMF and LBW formula group, 6 babies were observed to have pre-feed residue in HMF and 12 babies in LBW formula group. Vomiting was observed in 4 babies in HMF group and 16 babies in LBW formula group. Abdominal distension was observed in 4 babies in HMF and 6 babies in LBW formula group. Necrotizing enterocolitis was observed in 4 babies in LBW formula group while none in HMF group as shown in Table 5.

Table 5: Feed intolerance-HMF vs LBW Formula group

Side effects	HMF		LBW		p value
	N	%	N	%	
Prefeed residue	6	13	12	26	0.27
Vomiting	4	8.7	16	34.8	0.03
Abdominal distension	4	8.7	6	13	0.64
NEC	0	0	4	8.7	0.15
Total	14		38		

The incidence of prefeed residue, abdominal distension and NEC was more in LBW formula group as compared to HMF group. This difference did not reach levels of statistical difference.

However vomiting was observed to be more in LBW formula group as compared to HMF group and the result was statistically significant(p=0.03).

Cost Comparison- HMF vs LBW Formula Group: The per patient cost was compared between HMF vs LBW formula group. It was observed that cost of feed fortification per patient/day in LBW formula group was observed to be Rs. 10.60/- whereas the cost was about Rs.262/- in HMF group. The average cost per patient during study period was significantly more in HMF group as compared to LBW formula group and the difference was statistically highly significant (p<0.0001).

Discussion

This study was a randomized control trial wherein we compared the effect of feed fortification with human milk fortifier vs low birth weight formula on weight gain, time taken to regain birth weight and side effect profile in both groups.

It was seen in our study that the distribution of the study groups viz. HMF vs LBW formula fortification of expressed breast milk was well matched for gender, gestation age and birth weight categories which is similar to study done by Mukhopadhyay et al[7] where there was no statistically significant difference in the distribution of these variables.

The result in our study established an earlier time taken to regain birth weight in the HMF group than LBW formula group though the difference did not reach level of statistical significance.The studies done by Zuppa et al,[8] Porcelli P et al[9] and Reis BB et al[10] have shown similar results of earlier weight gain by human milk fortifier enrichment of breast milk. In these studies the control group was taken to be expressed breast milk without fortification. On further analysis, it was observed that the mean time taken to regain birth weight in both groups across various gestation ages was

not statistically significant. However, in the term babies, HMF group regained birth weight significantly quicker than the LBW formula group.

In our study, the secondary outcome measure in the form of pre-feed residue, vomiting, abdominal distension and NEC was observed to be more in LBW formula group as compared to HMF but the difference was found to be statistically not significant. Vomiting however was more in LBW formula group and the difference reached the level of statistical significance(p=0.03). In the study done by Gathwala et al[(11)] the incidence of side effects in the form of vomiting and percentage aspirates per day was comparable between the EBM+HMF and only EBM group and the result was statistically not significant.

In the study on human milk fortification vs preterm formula feeds in preterm neonates done by Sakka et al,[(12)] the incidence of feed intolerance and NEC was less in HMF group which is similar to our study.

In our study the average cost per patient for multinutrient fortification is Rs.10/day for LBW formula group and Rs.262/day for HMF group. This considerable difference in cost per patient is an important factor while deciding choice of feed fortification in developing countries like ours. The analysis of cost wise comparison to the best of our knowledge has not been addressed in any of the trials so far.

Conclusion

Our study suggests that the supplementation with human milk fortifier is as efficacious as low birth weight formula in expressed breast milk with regards to weight gain, mean calories and protein provided as well as NPC/N.The marginal benefit of increased weight gain and protein accretion is offset by considerable difference in cost where collectively, LBW formula is much cheaper as compared to HMF. This factor holds considerable importance in developing countries. The tolerance was found to be better in HMF group. The results however did not reach the levels of statistical significance except vomiting which was observed more in LBW formula group. The limitation of this study is its small sample size. A larger multicentric study would reinforce the usefulness of breast milk fortification with HMF vs LBW formula and also delineate the tolerability of both.

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