

Human Milk Fortifier with Higher Energy for Preterms: Beneficial or Not?

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BACKGROUND/AIMS

Human milk(HM) is considered to be the best nutrient for premature infants, it is usually inadequate to support the appropriate growth rate and it is frequently supplemented with a human milk fortifier to supply more energy and other nutrients. However, in spite of this supplementation, some infants still fall short of the expected growth rate. Additional calories provided by maltodextrin could help such infants to grow better was hypothesised in this research.

MATERIAL and METHODS

Preterms of less than 34 weeks of gestation and weighing less than 1500 g, were evaluated. The infants were randomly placed into two groups while receiving 100 ml/kg human milk. Group 1 infants received human milk mixed with protein and Group 2 infants received human milk mixed with protein plus maltodextrin. This regimen continued minimum 15 and maximum 29 days and the body weight, height and head circumference measurements were recorded.

RESULTS

A total of 187 preterm infants were analysed, 46 infants were excluded from the study, while the remainder were randomly placed into two groups, respectively. Their gestational age, birthweight, first day of nutrition, consumption and duration of feedings were all comparable. There were no significant differences between their weight, height and head circumference gains on the 28th day. There were also no significant differences between their serum blood urea nitrogen, albumin, calcium, phosphorus, alkaline phosphatase, sodium, potassium, chloride, thyroid stimulating hormone and free T4 levels.

CONCLUSION

Although the addition of HMF increases weight gain in premature infants, the added calories do not provide any statistically significant but better growing patterns.

Keywords: Calorie, fortification, growth rate, preterm, protein

INTRODUCTION

Body and Brain development are crucial for newborns, particularly for preterm infants, therefore inadequate feeding during the developmental period can negatively affect the short- and long-term outcomes. Therefore, adequate feeding is essential for preterm infants for optimal growth (1- 4).

The postnatal growth rates of preterm infants should be the same as the intrauterine growth rate (3). The American Academy of Pediatrics (AAP) and the World Health Organization recommend breast milk for all newborns (5, 6). However, the inadequate protein and mineral intake from breast milk by preterm infants has previously been documented, and most of the time it is not sufficient to maintain the appropriate growth rate (7, 8). Therefore, breast milk is frequently enriched with a breast milk fortifier to provide more energy and other nutrient supplements. According to recommendations of the AAP and the ESPGAN, the protein intake of preterm babies should be increased to 4–4.5 gr/kg/day (3, 4). In addition to protein intake, calorie requirements are also higher for preterm babies according to the same recommendations (3, 4). Moreover, breast milk calorie intake may be inadequate to meet the required daily amount of 105–135 kcal/kg/day for preterm babies (3, 4).

Although breast milk fortifiers provide more energy and protein than breast milk alone, they may not provide adequate growth requirements for preterm babies. Increasing the volume of milk to be consumed may also cause hypervolemia in preterm infants. In this study, we investigated whether increasing the calorie intake of preterm infants from 77kcal/100 mL to 99 kcal/100 mL by adding fortifiers in breast milk would result in better growth rates.

MATERIAL and METHODS

This study was conducted at the Neonatal Intensive Care Unit between June 2009 and March 2010. The preterm infants included in the study were all small-for-gestational-age infants, less than 34 weeks of gestational age, and less than 1500 gr in birth weight. One hundred and eighty-seven preterm infants were evaluated. Infants who: had congenital anomalies, suffered perinatal asphyxia, had undergone a major surgical operation, had sepsis, were not feeding exclusively on breast milk were excluded from the study. The study was approved by the Ethics Committee of the Hospital (No:24/04/2009-28) and written informed consent was obtained from the parents of the infants included in the study.

All the participants were weighed daily, while the height and head circumferences (HC) were measured weekly. Participants were monitored for at least 15 days or until they were 29 days old. All participants were fed breast milk only and daily intakes were increased by 20 ml/kg/day until the infant received up to 200 ml/kg. Once the participants were receiving up to 100 ml/kg of breast milk, they were randomly assigned to two groups. Group 1 infants, the control group, received breast milk mixed with HMF (Eoprotin) in a ratio of 1 spoon per 30 mL; while Group 2 infants, the study group, received breast milk mixed with HMF (Eoprotin) in a ratio of 1 spoon per 30 ml in addition to ½ a spoon of maltodextrin powder (Fantomalt) per 30 mL. Following the enrichment of the breast milk in two distinct ways, the caloric intake for Group 1 was 77 kcal/100 mL and 99 kcal/100 mL for Group 2. Blood urea nitrogen (BUN) calcium, magnesium, alkaline phosphatase, sodium, potassium, and chloride levels were monitored on the 5th day, 15th day, and 29th day. Thyroid-stimulating hormone (TSH) and free T4 levels were checked on the 10th day of life. In addition, gastrointestinal side effects (abdominal distension, gastric residue, vomiting, feeding intolerance, diarrhea), allergy, sepsis, and other problems were noted.

Statistical Analysis

Statistical analysis was performed using the NCSS 2007 software for Windows. Continuous variables were expressed as mean ± standard deviation of the mean (SD). The results of the two groups were compared using Student’s t-test for normally distributed data. To determine the relationship between principal variables and the other continuous variables, Pearson correlation or Spearman non-parametric correlation tests were

used. When equality of variances was not present, Kruskal Wallis and Mann–Whitney U non-parametric tests were used. Values of p<0.05 were considered statistically significant.

RESULTS

Subjects

The study was initially performed on 187 preterm infants aged 6–16 days. However, 10 infants were excluded from the study for not taking adequate breast milk. Furthermore, 35 infants were excluded because of side effects, while 1 infant was transferred to another hospital. Seventy-one preterm babies were enrolled into Group 1 (51% girls, 49% boys) and 70 preterm babies were enrolled into Group 2 (43% girls, 57% boys). Gestational age, birth weight, sex, onset of enteral feeding, maximum feeding volume, first day of fortification, and duration of fortified feeding in days were not significantly different between groups (Table I). The mean age at first enteral feeding (in days) was 1.9±0.47 days in Group 1 and 1.95±0.21 days in Group 2, while the first day of fortification was 10.94±4.39 days in Group 1, and 10.4±4.39 days in Group 2. Participants were fed for 23.96±6.62 days in Group 1 and 21.33±7.55 days in Group 2 with fortified breast milk.

The volume of intake of the modified breast milk by participants in both groups was maintained around the target volume of 180-200 mL/kg/day.

Growth

The weight gain of Group 1 participants and Group 2 participants was 31 mg/kg/day and 32 mg/kg/day respectively on the 14th day of fortification; 32 mg/kg/day and 35 mg/kg/day respectively on the 28th day of fortification. Although an increase in weight gain was noted in Group 1 participants, there was no statistical difference between the two groups (p>0.005). (Figure 1)

TABLE I. Demographic and feeding characteristics of patients

| | Group 1 | Group 2 | p |
|-------------------------------------|---------------|----------------|-------|
| Gestational age (weeks) | 29.13±1.93 | 28.91±1.95 | 0.574 |
| Birthweight (g) | 1157.88±18932 | 1152.15±178.85 | 0.878 |
| Girl/boys (n/n) | 37/34 | 30/40 | 0.404 |
| First enteral feeding (day) | 1.9±0.47 | 1.95±0.61 | 0.605 |
| Maximum feeding (ml/kg/gün) | 196.78±6.66 | 198.15±3.56 | 0.249 |
| First day of fortification (day) | 10.94±4.96 | 10.4±4.39 | 0.584 |
| Duration of fortified feeding (day) | 23.96±6.62 | 21.33±7.15 | 0.076 |

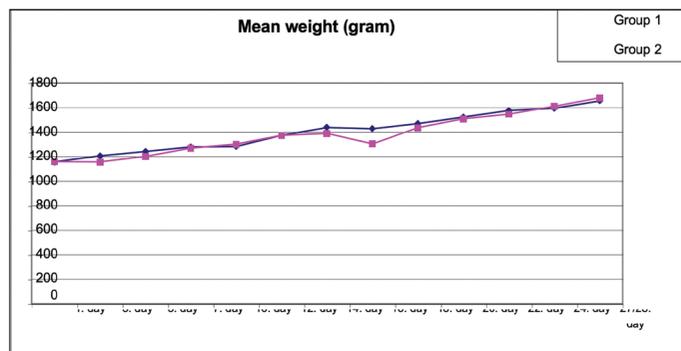


FIGURE I. Mean weights of groups

Main Points:

- Standard fortification techniques may not be adequate for providing enough energy and protein.
- Higher protein with higher calorie is essential for preterm growth.
- Increasing protein and calorie did not cause any gastrointestinal side effects.

Participants' mean height in both groups did not differ on the 1st day of fortification (37.237±2.32 cm in Group 1 and 37.55±2.13 cm in Group 2) (p>0.05). On the 12th day of fortification an increase in the height of participants by 1.55±0.78 cm/day for Group 1 participants and 1.31±0.72 cm/day for Group 2 participants (p>0.05). At the end of the study, there was no statistically significant difference between the mean height increase of participants in either group (2.44±1.11 cm/day in Group 1 and 2.16±1.21 cm/day in Group 2) (p>0.05). (Figure 2)

At the end of the study, Group 2 participants had a significantly higher HC. (p=0.014). The mean HC was 27.52±2.15 cm in Group 1 and 27.34±1.56 cm in Group 2 (p>0.05). An increasing rate in

HC was not noted, 1.29±0.63 cm/day in Group 1 and 1.38±0.7cm/day in Group 2 on the 12th day of fortification. HC measurements were 3.19±0.79 cm/day in Group 1 and 3.89±1.15 cm/day in Group 2 on the 28th day of fortification (p=0.014). (Figure 3)

Serum Biochemical Data

There was no statistically significant difference between the levels of BUN, albumin, TSH, free T4, phosphorus, magnesium, alkaline phosphatase, sodium, chloride, and potassium levels on the 1st, 14th, and 28th day of fortification (p>0.05). However, although calcium levels in Group 2 participants were significantly higher, they were still within the normal ranges for preterm babies (p=0.016).

Feeding Tolerance and Clinical Course

Associated side effects among the participants were not statistically significant between the two groups (Table 2). In fact, there were no statistically significant differences in any of the variables compared between the two groups. Three infants in Group 1 had gastric residue and 4 had abdominal distention (p>0.05). Three infants from Group 1 and 2 from Group 2 had feeding intolerance (p>0.05). Vomiting was only noted in 3 participants from Group 1 (p>0.05).

Apnea was not documented among Group 2 participants but was noted with 4 participants in Group 1 (p>0.05). Five participants from Group 1 and 3 from Group 2 had sepsis (p>0.05). Two participants, one from each group, had necrotizing enterocolitis (p>0.05).

TABLE 2. Side effects

| Side effect | Group 1 | Group 2 | p |
|----------------------|-------------|-------------|-------|
| Gastric residual | 3 4.23% | 0 0.00% | 0.179 |
| Abdominal distention | 4 5.71% | 0 0.00% | 0.098 |
| Feeding intolerance | 3 4.29% | 2 2.86% | 0.632 |
| Apnea | 4 5.71% | 0 0.00% | 0.098 |
| Vomiting | 3 4.29% | 0 0.00% | 0.179 |
| Sepsis | 5 7.14% | 3 4.29% | 0.491 |
| NEC | 2 2.86% | 2 2.86% | 0.930 |
| Hypercalcemia | 7 9.86% | 4 5.71% | 0.577 |
| Total cases | 26 (36.61%) | 20 (28.58%) | 0.551 |

NEC: necrotising enterocolitis

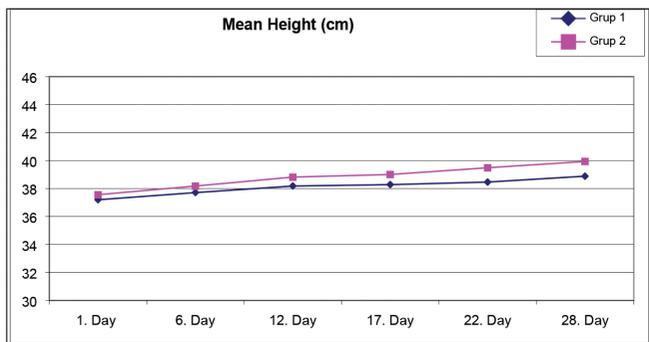


FIGURE 2. Mean heights of groups

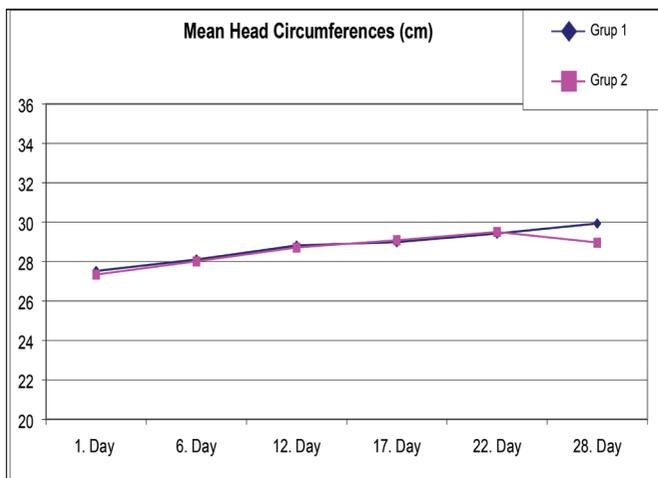


FIGURE 3. Mean head circumference of groups

DISCUSSION

The AAP and the ESPGAN recommend the fortification of breast milk to increase the growth rate of preterm infants. Different fortification strategies were recommended to correct inadequacies in both the quality and quantity of protein and calorie concentrations of FHM. (3, 4) Standard fortification techniques may not be adequate for providing adequate energy and protein. Increasing the intake of milk may cause hypervolemia problems in preterm infants. Therefore, in order to prevent this, we added an energy provider to standard fortification to increase the caloric amount in HM. In this randomized prospective controlled trial conducted with 187 preterm infants, energy intakes were increased from 77kcal/L to 99 kcal/L; and infants' growing rate, biochemical results, and possible side effects were monitored. Adding an energy provider to HM may increase osmolarity and cause feeding intolerance and Necrotising Enterocolitis (NEC). However, there was no difference between the two groups with regards to gastrointestinal side effects. In addition, the rate of sepsis was similar in both groups. Infants provided with HMF supplemented with an energy provider had an improved growth rate, weight and height gain, and an increase in HC measurements when compared with the infants who were only given HMF.

In a previous study (9), two different protein-containing fortification techniques were compared using preterm infants whose weight was less than 1250 gr and had a weight gain of less than 15/ gr/kg/day as the subjects. Daily weight gain was reported to be 17.0±2.0 gr/kg/day in the group given 3.5 gr/kg/day of protein and 11.5±4.8 gr/kg/day in the group given 3 gr/kg/day of protein at the 4th week of fortification. However, in the current study, the infants in Group 1 were given fortified breast milk at 10.94±4.96 days and Group 2 at 10.4±4.39 days. Growth rates were found to be 33±22 gr/kg/day for the Group 1 infants and 35±27 gr/kg/day for the Group 2 infants. The difference in the recorded growth rates between

the preterm infants in the current study and the participants in the Brummer study may have resulted from the fact that in the current study protein-rich milk was given at an earlier age.

In a study by Mukhopadhyay et al. (10), 166 preterm infants were examined, and 2 different calorie-containing milk products were compared (66 kcal/100 mL to 79 kcal/100mL). Participants were given 150/mL/kg/day until they weighed 2000 gr. The fortified milk-fed group was followed up to 31.9±16.2 days and the only-breast-milk-fed group was followed up to 29.4±13.2 days. In this study, the reported growth rate was 15.1±6 gr/kg/day in the higher-calorie-given group and 12.9±4 gr/kg/day in the control group. We reported 33±22 gr/kg/day in the control group (Group 1) and 35±27 gr/kg/day in the study group (Group2). Our preterm infants had a higher weight gain because fortification of milk products occurred earlier. In addition, the reported increase in height was 1.04±4 cm/week in the control group and 0.86±0.2 cm/week in the study group. Among the preterm infants in this study, the increase in height was observed to be 0.61±0.78 cm/week in the control group and 0.54±0.30 cm/week in the study groups. The difference in height measurements between the two studies may be due to ethnic differences.

According to the study conducted by Aslanoglu et al. (11), breast milk was fortified in three steps. Initially, 1.9 gr/100 mL during the study in the control group and 1.9 gr/100 mL of breast milk in the 1st week, 2.2 gr/100 mL of breast milk in the 2nd week, and 2.3 gr/100 mL of breast milk in the 3rd week in the study group were added when preterm babies were taking 100 mL/kg/day enteral feeding and excessive breastmilk was given to the babies in the control group. Weight increase rates were reported as 24.8±4.8 gr/day in the control group and 30.1±5.8 gr/day in the study group. In the current study, comparatively, these rates were noted as 38.65±7.56 gr/day in the control group and 41.37±6.29 gr/day in the study group. The difference in weight gain by the preterm infants between the two studies may have resulted from the preterm infants' increased protein consumption, which is 3 gr/kg/100 mL from the 1st day of fortification.

In this prospective, randomized controlled study, differences in either weight gain or rate of increase in height between the two groups of preterm infants were not statistically significant. However, the higher-energy-consuming group (Group 2) displayed an increase in height and weight by the end of the study, in addition to an improved HC increase rate. Side effects, especially gastrointestinal side effects, Necrotizing Enterocolitis, and feeding intolerance rates were comparable in both groups.

In conclusion, despite the better growth pattern of the higher-calorie-given group, the main factor required for the growth of preterm infants is higher protein intake. As a result of this, higher protein with higher-calorie diets are essential to achieve the same growth ratio as in utero growth in the nutritional management of preterm babies. Amino acids are important in the synthesis of insulin, insulin-like factors, and other growth-related hormones and it is reported that the lower-protein-given group shows slower growth (12-16).

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Zeynep Kamil Women Health and Children Diseases Training and Research Hospital (28-24/04/2009).

Informed Consent: Written informed consent was obtained from patient who participated in this study

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.D, F.O.; Design - C.D, F.O.; Supervision - F.O.; Resources - C.D, F.O.; Materials - C.D.; Data Collection and/or Processing - C.D.; Analysis and/or Interpretation - C.D, F.O.; Literature Search - C.D, F.O.; Writing Manuscript - C.D, F.O.; Critical Review - C.D, F.O.

Conflict of Interest: Authors have no conflicts of interest to declare.

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