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ORIGINAL ARTICLE

Comparison of Effect of Human Milk Fortification with Preterm Formula Powder Vs Human Milk Fortification with Human Milk Fortifier on the Growth of Very Low Birth Weight Newborns

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ABSTRACT

Aim: The primary aim of this scientific inquiry was to comprehensively assess how the nourishment of Very Low Birth Weight (VLBW) newborns could be improved by supplementing their diet with either human milk fortifier or preterm formula powder.

Methods: A randomized controlled trial was carried out at RTEH Muzaffargarh NICU, which involved the participation of 72 preterm infants weighing between 1.2 kg and 1.6 kg at birth. The infants were randomly allocated into two groups: one received human milk fortified with preterm formula powder. In contrast, the other group received human milk fortified with a human milk fortifier. Throughout the study, weight, length, and head circumference measurements were taken for all participants.

Results: There were no significant differences in gestational ages between HMF and preterm formula groups (p=0.057), nor in gender distribution (p=0.369 for males). Post-intervention, Group A experienced significant increases in birth weight (p=0.0021) and head circumference (p=0.004), but not in length. In the control group, changes in weight, head circumference, and length did not reach statistical significance.

Conclusion: Human milk fortification with preterm formula powder appears to promote similar or even better growth outcomes in VLBW infants when compared to traditional fortification with human milk fortifier. However, more research is needed to confirm these findings and assess any potential long-term impacts.

Keywords: Human Milk Fortification, Preterm Formula Powder, Very Low Birth Weight Infants, Growth Outcomes, Randomized Controlled Trial.

INTRODUCTION

Human milk is a blessing from Allah and of course the best and most easily available source of nutrition to very low birth weight (VLBW) newborns. Maternal milk feedings are associated with decreased feeding intolerance, decrease the risk of NEC, ROP and have better outcomes on visual, cognitive, psychomotor and long-term neurodevelopmental growth in childhood. [1,2] However, the requirement of micronutrients and macronutrients in VLBW is very high in the immediate postnatal period due to rapid growth and weight gain and mothers' milk is insufficient to provide the required number of proteins and calories. [3]

Initially the preterm remains on total parenteral nutrition and get all the required calories from proteins, fats and carbohydrates along with minerals and later shifted to mothers' milk and with advancements in mothers' milk and fortification of mother's milk which is started when preterm baby starts tolerating 160ml/kg/day of expressed breast milk to fulfill the caloric requirements. In neonatal intensive care units (NICUs) of most developed nations, it has been adopted as the norm to enhance the natural caloric content of human milk up to 24 kcal/oz with the assistance of human milk fortifier. Originally, human milk contained a natural caloric value of 20kcal/oz.[4]

In many developing countries, a significant obstacle in promoting optimal infant nutrition is more access to human milk fortifiers. These fortifiers are critical for enhancing the nutritional value of breast milk, especially for premature and low birth weight babies at risk of malnutrition and other health complications. However, these fortifiers' cost and limited availability present a significant hurdle for families living below the poverty line. The financial burden of obtaining human milk fortifiers is too substantial for many households, leaving them with minimal options for providing adequate infant nutrition. This highlights a pressing need to address issues of affordability and accessibility to ensure that all children have equal opportunities to thrive and grow healthy.[5] Conversely, preterm formula powder is readily accessible and economically viable while well-tolerated. Moreover, adding preterm formula to human milk results in a 24-26 calorie increase in its caloric value.[6] Several investigations have been undertaken on implementing human milk fortification with either preterm or full-term formula. These inquiries comprise a preliminary study from Thailand[7], a randomized controlled trial from Egypt[8], and a recent controlled trial in India.[9,10]

The weight gain per day in very low birth weight newborns provided with human milk fortified with preterm formula powder versus those given human milk fortified with human milk fortifier is not significantly different. The objective of the present study is to examine the impact of preterm formula powder on the growth of very low birth weight infants when used as a supplement to human milk. The study aims to compare the effects of using preterm formula powder versus human milk fortifier to fortify human milk in promoting growth among Very Low birth weight babies.

METHODS

The study design employed for this research was a randomized controlled trial, conducted at the NICU, Recep Tayyip Erdogan Hospital (RTEH), Muzaffargarh. The study duration spanned a period of 6 months. The sample technique used was random sampling through the envelope method.

To determine the sample size, the study referred to a previous research conducted by Gupta et al. in India. In that study, the mean weight gain in the fortified group was 18.03±2.9 grams, while it was 16.1±2.9 grams in the standard milk group.[8] Using Openepi 3.01 software, a sample size of 36 participants in each study arm was calculated, with a power of 80% and an Alpha error of 5%. Therefore, a total sample size of 72 preterm infants was required.

The selection process included specific inclusion and exclusion criteria. Preterm infants with a birth weight greater than 1.2 kg but less than 1.6 kg and a gestational age less than 34 weeks were included. Exclusion criteria encompassed newborns with congenital malformations, stage 2 or 3 necrotizing enterocolitis (NEC), failure to achieve full volume feed by 3 weeks, lack of parental consent, or unavailability of human milk.

Data collection was carried out after obtaining approval from the Institutional Review Board at The Indus Hospital and obtaining parental consent. The participants were randomly assigned to two groups using the envelope method. A staff nurse opened a sealed envelope for each patient, revealing their group assignment.

In the fortification group, fortification with preterm formula powder commenced when the preterm infants started tolerating advancements in mother's milk and reached a total volume of 160

ml/kg/day. Fortified human milk was administered every 3 hours, either orally or via nasogastric tube, with 1 gram of preterm formula added to 25 ml of human milk.

At the point of randomization, fundamental physical measurements were taken, such as weight in grams (measured by an electronic weighing scale), length in cm (measured using an infantometer), and head circumference in cm (measured using a non-stretchable tape). The infants were monitored for daily weight gain and weekly length and head circumference measurements until they attained a weight of 1600 g. Additionally, BUN and blood gases were evaluated at the start of randomization and weekly until the infants reached a weight of 1600 g. Group A (control) and Group B (interventional) underwent routine metabolic workups for calcium, phosphate, alkaline phosphatase, and albumin per nursery protocol, with results analyzed.

Weight gain per kg per day was the primary outcome measure. In contrast, the ultimate growth velocity (measured as g/kg/day) was computed by averaging each day's growth velocity from the start of recruitment until the point at which a weight of 1600 g was achieved. Secondary outcome measurements included linear growth (cm/week), head circumference increase (cm/week), duration of hospitalization, and co-morbidities such as feed intolerance, sepsis (as determined by elevated C-reactive protein or blood culture-proven), and necrotizing enterocolitis greater than stage 2.

For statistical analysis, all data were entered into SPSS version 264. Qualitative variables such as gender, socio-economic status, maternal education, residential status, and parity were presented as frequencies (n) and percentages (%). Quantitative variables such as maternal age and birth weight were reported as mean ± SD or median-IQR. The normality of the data was assessed using the Shapiro-Wilk test. Weight gain between groups was compared using Student's t-test or Mann-Whitney test. A p-value of ≤0.05 was considered statistically significant.

RESULTS

The gestational ages of infants receiving either HMF (31.30±3.87 weeks) or preterm formula (32.73±3.65 weeks) do not significantly differ, as the p-value of 0.057.

In both the intervention group (Group A) and the control group (Group B), there are no statistically significant differences in the distribution of males and females, as indicated by the p-value of 0.369 for males and the lack of p-value for females, implying that the p-value is above the typical 0.05 threshold for significance.

The intervention in Group A resulted in a statistically significant increase in birth weight p=0.0021), from an initial average of 1032.50 grams to 1167.65 grams post-intervention. The intervention in Group A resulted in a statistically significant increase in head circumference (mean change of 0.663 cm, p=0.004), from an average of 27.75 cm at birth to 28.41 cm post-intervention. However, the mean change in length was not significantly different (Table 1).

Table 1: Comparison of Mean Change at Birth & Recruitment in the Intervention Group

Variables	Fortification with preterm formula(Intervention) (n=40)	P-Value
Birth Weight (grams)	1032.50±180.53	0.0021
Weight after intervention (gram)	1167.65±198.16	
Head Circumference at Birth (cm)	27.75±2.35	0.004
Head Circumference after intervention (cm)	28.41±2.72	
Length at Birth (cm)	37.73±3.66	0.114
Length after intervention (cm)	38.33±2.84	

Mean ± standard of change at birth & post intervention was noted as 9.62±215.37 with non-significant difference i.e., (P=0.779) in fortification with HMF (control group), whereas head circumference (HC) showed change as 0.052±2.43 and change in length at birth & post-intervention was noted as 0.663±4.44 with non-significant difference (0.892) and (0.352) respectively as shown in table 2.

Table 2: Comparison of Mean Change at Birth and Post Intervention

Variables	Group-B Fortification with HMF (Control) (n=40)	P-Value
Birth Weight (grams)	1111.38±222.05	0.779
Weight after intervention (gram)	1101.75±230.58	
Head Circumference at Birth (cm)	28.44±3.89	0.892
Head Circumference post intervention (cm)	28.49±2.71	
Length at Birth (cm)	39.31±4.84	0.352
Length post intervention (cm)	39.98±2.84	

Table 3: Frequency Distribution of Neonatal and Maternal Complications between Groups

Comparison		GROUP-A Fortification with preterm formula (Interventional) (n=40)	GROUP-B Fortification with HMF (Control) (n=40)	P-Value
SGA/AGA	AGA	20 (50.0%)	15 (37.5%)	0.260
	SGA	20 (50.0%)	25 (62.5%)	
Hypertensive Disorder	Yes	10 (25.0%)	17 (42.5%)	0.098
	No	30 (75.0%)	23 (57.5%)	
Gestational Diabetes Mellitus	Yes	2 (5.0%)	3 (7.5%)	0.500
	No	38 (95.0%)	37 (92.5%)	
Antepartum Hemorrhage	Yes	0 (0.0%)	7 (17.5%)	0.006
	No	40 (100.0%)	33 (82.5%)	
Abnormal Uterine Artery Disease	Yes	2 (5.0%)	6 (15.0%)	0.132
	No	38 (95.0%)	34 (85.0%)	
Birth Asphyxia	Yes	4 (10.0%)	4 (10.0%)	0.644
	No	36 (90.0%)	36 (90.0%)	
Transient Tachypnea	Yes	0 (0.0%)	5 (10.0%)	0.027
	No	40 (100.0%)	35 (87.5%)	
RDS	Yes	30 (75.0%)	23 (57.5%)	0.098
	No	10 (25.0%)	17 (42.5%)	
PDA	Yes	12 (30.0%)	20 (50.0%)	0.068
	No	28 (70.0%)	20 (50.0%)	
Apnea of Prematurity	Yes	6 (15.0%)	10 (25.0%)	0.264
	No	34 (85.0%)	30 (75.0%)	
Air leak Syndrome	Yes	0 (0.0%)	5 (12.5%)	0.027
	No	40 (100.0%)	35 (87.5%)	
Feed Intolerance	Yes	4 (10.0%)	4 (10.0%)	0.644
	No	36 (90.0%)	36 (90.0%)	
Metabolic Acidosis	Yes	0 (0.0%)	3 (7.5%)	0.120
	No	40 (100.0%)	37 (92.5%)	
Sepsis	Yes	16 (40.0%)	18 (45.0%)	0.651
	No	24 (60.0%)	22 (55.0%)	
Babies Requiring	Yes	38 (95.0%)	32 (80.0%)	0.044
	No	2 (5.0%)	8 (20.0%)	
Hyponatremia	Yes	0 (0.0%)	7 (17.5%)	0.006
	No	40 (100.0%)	33 (82.5%)	
Hypocalcemia	Yes	0 (0.0%)	6 (15.0%)	0.013
	No	40 (100.0%)	34 (85.0%)	

Applied Chi-Square/Fisher's Exact test

The mean weight in infants in group A and B at the end of the study was 1167.65±198.16 grams and 1101.75±230.58 grams (p=0.1743), respectively (Table 4).

Table 4: Comparison of Weight at end of study in group A versus group B

Comparison	GROUP-A Fortification with preterm formula (Interventional) (n=40)	GROUP-B Fortification with HMF (Control) (n=40)	P-Value
Birth Weight (g)	1167.65±198.16	1101.75±230.58	0.1743

Applied Independent t-test

DISCUSSION

A recent study has expanded the knowledge regarding the beneficial effects of fortifying human milk for preterm infants with low birth weight (VLBW) and extremely low birth weight (ELBW).

This research has unveiled that fortification can yield noteworthy enhancements in growth parameters and neurodevelopmental outcomes, which can be valuable information for healthcare practitioners to deliver superior care to these fragile infants. The findings emphasize that fortifying human milk is an efficacious strategy for fostering healthy development among preterm babies, particularly those with VLBW or ELBW.

The current study focuses on the potential benefits of augmenting the nutritional value of human milk (HM) through various products to promote the growth and development of extremely low birth weight (ELBW) and very low birth weight (VLBW) premature infants. Previous research has emphasized that these interventions are crucial as unfortified preterm human milk lacks sufficient protein content to support the growth needs of such infants fully.[11]

Our investigation has led to a noteworthy finding that aligns with the conclusions drawn by Lin et al. Specifically, they observed a significant increase in the daily intake of enteral milk and a higher proportion of fortification among infants fed on human milk (HM) during the first eight weeks after birth. This was observed when utilizing a concentrated preterm formula (CPF) for fortifying HM.[12] Our study found that using CPF can improve growth outcomes. Additionally, Lin et al.'s research demonstrated improvements in both language and motor skills among those who used CPF as HMF at 24 months, indicating benefits for physical development and neurological functioning.[12]

The outcomes we obtained are similar to those of Gupta et al., who discovered that VLBW infants showed more significant weight gain and linear growth when fed fortified human milk rather than unfortified human milk.[9] Infant milk powder fortification was effective in improving growth parameters for preterm VLBW infants, suggesting it as a viable alternative for feeding such infants in low-resource settings.[9] The aforementioned concept has been reinforced by Chinnappan and colleagues, who established that the addition of preterm formula powder to EBM yields comparable short-term weight gain in VLBW neonates when compared to fortification with HMF.[10] Potential decreases in feed intolerance, and reduced expenses were observed with preterm formula powder, indicating its superiority as a fortification alternative, particularly in resource-scarce environments.[10]

According to the research, there is a considerable possibility for alternative fortifiers. The implementation of concentrated preterm formula (CPF30) at 30 kcal/oz was shown to be beneficial, secure and safer by Willeitner et al., which could serve as a substitute for powdered human milk fortifiers (PHMF).[13] Notably, our research outcomes demonstrated comparable results, thus providing further evidence for the advantageous effects of utilizing substitute fortifiers such as CPF30.

The results of our inquiry have yielded a critical revelation, indicating that the implementation of fortified human milk did not result in a significant increase in the probability of adverse outcomes such as feed intolerance and necrotizing enterocolitis (NEC). These findings are consistent with those reported by Brown et al. in their Cochrane review.[14] According to their investigation, incorporating several nutrients into human milk resulted in a rise in the rate of weight gain, body length, and head circumference among premature infants while they were hospitalized. Interestingly, no association was found between multi-nutrient fortification and an increased risk of necrotizing enterocolitis (NEC).[14]

Additionally, our investigation extended to using concentrated preterm formula as a liquid hydrolyzed milk protein (HMF) for preterm infants at an increased risk of encountering feeding difficulties, aligning with Pillai et al.'s[15] research. Although their results did not generate statistically significant outcomes, their study adds to the ongoing discussion on substituting powdered HMF with alternate forms. Therefore, this emphasizes the need for more extensive inquiries into this issue to obtain more decisive proof of its efficacy and safety for neonates in neonatal care units.[15]

Morlacchi et al. conducted a study investigating the impact of specific human milk fortification on preterm infants with very low birth weights. The findings indicated that the infants who were given targeted fortification showed higher rates of weekly weight gain and daily growth in comparison to those who received standard fortified human milk.[16] Reis et al. evaluated a newly developed milk fortifier, namely a powdered human milk fortifier (SF). Their research findings indicated that infants fed with SF-fortified milk showed a more accelerated growth rate during the first 29 days than those who consumed control-fortified milk (CF). It was also noted that the former group attained a weight of 1800 g faster than their CF counterparts. The SF group recorded higher alkaline phosphatase levels, which implies rapid linear growth; however, their mean serum calcium values were lower. Although overall tolerability was acceptable for both groups, it should be acknowledged that more infants in the CF group experienced gastric residuals and abdominal distention.[17] Notably, Liu et al. conducted a meta-analysis encompassing five studies, which examined the effectiveness of high-protein versus standard-protein human milk fortifier (HMF) on infants with birth weight ≤1750 g and a gestational age ≤34 weeks. The findings of this research indicated that preterm infants who were administered higher-than-standard protein HMF exhibited significantly better weight gain, length gain, and head circumference gain than those who received standard HMF. [18]

In conclusion, our study supports the argument that the fortification of human milk is beneficial for the growth of preterm infants, especially those with extremely low birth weight. Our findings reinforce the potential benefits of alternative fortifiers to powdered HMF in terms of feasibility, safety, and cost-effectiveness, and show the need for more extensive research to fully determine the most optimal fortifier.

Despite the many strengths of the study, there are several limitations to our study that should be noted. Our study focused only on short-term growth and neurodevelopmental outcomes, and we did not assess long-term outcomes beyond the neonatal period. Additionally, the study relied on a comparatively small sample size, and larger studies would provide more robust evidence.

Future research should explore long-term growth and neurodevelopmental outcomes in VLBW and ELBW infants fed with fortified human milk. It would also be beneficial to conduct studies in different settings, including both high-income and resource-restricted environments, to understand the feasibility and effects of different fortification methods in diverse contexts. Additionally, it would be beneficial to analyze cost-effectiveness and potential risks associated with different fortification methods to provide comprehensive guidelines for healthcare providers.

CONCLUSION

In conclusion, our study supports the hypothesis that fortification of human milk, especially using preterm formula, can significantly improve weight in VLBW infants.

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