



ORIGINAL ARTICLE

Adverse effects of human milk fortifier on preterm neonates in a neonatal intensive care unit of a tertiary care hospital, Karachi.

Hareem Syed¹, Azeem Khan², Faraz Ahmed³

Article Citation: Syed H, Khan A, Ahmed F. Adverse effects of human milk fortifier on preterm neonates in a neonatal intensive care unit of a tertiary care hospital, Karachi. Professional Med J 2024; 31(09):1347-1350. <https://doi.org/10.29309/TPMJ/2024.31.09.8222>

ABSTRACT... Objective: To determine adverse effects of Human Milk Fortifier on Preterm neonates in a Neonatal Intensive Care Unit. **Study Design:** Descriptive study. **Setting:** Indus Hospital NICU in Karachi. **Period:** Mar 2022 to September 2023. **Methods:** Aimed to investigate the adverse effects of HMF on 139 preterm neonates. The study excluded infants with congenital anomalies. Adverse effects, including Necrotizing Enterocolitis (NEC), metabolic acidosis, feeding intolerance, and other complications, were monitored. **Results:** The findings revealed that feeding intolerance was the most common adverse effect of HMF. Mild metabolic acidosis and NEC were also observed. These results are consistent with previous studies and may be attributed to the high osmolality of feeds following fortification with HMF. Despite the well-established role of HMF in promoting weight gain in preterm infants, the study underscores the importance of closely monitoring its use. **Conclusion:** Careful consideration of the potential risks and benefits of HMF is essential before prescribing it to preterm neonates. Future research with larger sample sizes and controlled designs is needed to validate these findings and explore strategies to mitigate the adverse effects of HMF in NICU settings.

Key words: Human Milk Fortifier, Preterm Neonates.

INTRODUCTION

Pakistan ranks high in neonatal mortality now days. Less than 37 weeks' gestation is labelled as prematurity, which is further categorized into extremely preterm, very preterm, moderate and late preterm based on gestational age.¹ Premature babies have prolonged stay in NICU after birth and can be compromised because of poor weight gain, infection, and other complications of prematurity.²

Breast milk fortifier is a powder that provides extra calories in the form of protein and vitamins. It is provided to preterm babies with either less than 34 weeks of gestation or less than 1500 grams to enhance growth and shorten NICU duration. One sachet is composed of protein- 0.4 grams, fat-0.2 grams, Carbohydrate- 0.3 grams and contains 4 Kcal/ sachet. Studies have shown drastic change in weight gain with the supplemental use of Human Milk Fortifier.³ Average weight gain with

HMF in 8-14 days is 32.2% as compared to those who did not receive HMF. Studies have shown that HMF improves anthropometry (weight, length, and head circumference). The other benefits are good neurological outcomes, and enhanced bone mineralization ($p < 0.001$). HMF contains protein as a major component and addition of it in human milk results in an increased amount of protein that causes renal solute overload. This can be identified simply by urea level in serum. Preterm infants fed breast milk + HMF are at risk for hyponatremia due to the limited sodium content of these feeds and increased urinary sodium losses.⁴

The studies have documented some adverse effects of HMF. These include feeding intolerance, bowel obstruction (23%)^{7,8} mild metabolic acidosis (20-30%) with inappropriate dosing, calcium stone ileus (10%), necrotizing enterocolitis (10%) and intestinal calculi (milk curd syndrome). By

1. BS Nutrition and Dietetics, Clinical Nutritionist/Dietitian, The Indus Hospital and Health Network.

2. FCPS (Pediatrics), FCPS (Neonatology), Junior Consultant Neonatology, Sindh Institute of Child Health & Neonatology.

3. FCPS (Pediatrics), FCPS (Neonatology), Junior Consultant Neonatology, Sindh Institute of Child Health & Neonatology.

Correspondence Address:

Dr. Faraz Ahmed
Sindh Govt. Hospital Korangi-5, Landhi Rd,
Sector 35 E Landhi Town, Karachi.
faraz_ahmed55@hotmail.com

Article received on: 22/04/2024

Accepted for publication: 25/07/2024

adding HMF the osmolarity is increased which is responsible for the above complications. These complications result in increased duration of stay in NICU, which ultimately increases expenses.⁵ Therefore, this study aims to observe such complications and determine the adverse effects of Human Milk Fortifier in neonates.

METHODS

This descriptive study was conducted in the NICU of the Indus Hospital Karachi over a period of 6-months after IRB approval (IRB/IHHN/IRB/2021/07/006). The study included 139 preterm neonates, \leq 37-weeks' gestation, either gender, admitted within 2-weeks after delivery through consecutive sampling. Premature neonates having congenital anomalies like congenital cardiac disease, surgical or renal, GI, pulmonary anomalies were excluded. The sample size of 139 preterm neonates was calculated for 10% frequency of necrotizing enterocolitis, at 95% confidence level and precision of 5%. Baseline characteristics i.e., age, gestational age, the birth weight was noted. HMF was added in EBM when the infant's daily feed reached target volume. Neonates were followed on a daily basis. Adverse effects like NEC, abdominal obstruction, milk curd syndrome, and metabolic acidosis were recorded on structured Performa.

Pre- necrotizing enterocolitis (NEC) was labelled as clinical suspicion in presence of non-specific signs and symptoms like abdominal distension, vomiting. Necrotizing enterocolitis was assessed clinically in presence of abdominal distension, vomiting and/or blood in stool. It was supported on X-ray finding which can be dilated gut, pneumatosis intestinalis, gut perforation. Bowel Obstruction was labelled on the basis of symptoms of bowel obstruction, persistent vomiting with or without bile-stained material, abdominal distension, increased gastric residuals before feeding and multiple air fluid levels on abdominal x-ray. Mild Metabolic Acidosis was assessed through arterial blood gas analysis. A serum pH < 7.35, and an abnormal serum bicarbonate concentration of < 22 mEq/L.

Data was entered and analyzed on software

STATA version 17. Frequencies and percentages were generated for qualitative variables while means and standard deviations were generated for quantitative variables.

RESULTS

From our study we found most of the children of 30-32 weeks of gestational age (50.3%) and 27-29 weeks (49.1%). Most of the infants had a birth weight of 1000-2000 grams (73.3%). We received almost equal genders infant with males at 50.3% and females at 49.7%. (Table-I) The majority of the admissions were through the emergency room 52.5%. In the complications observed among the infants NEC was found in a mere 2.1% of the sample population of infants, mild metabolic acidosis in 10%, and feeding intolerance was found in almost 32% of the infants. (Table-II) Interestingly other complications like calcium stones in ileum, bowel obstruction, and intestinal calculi were not found in any of the infants.

Variable	n(%)
Gestational age (weeks)	
18-26 weeks	9(6.4)
27-29 weeks	60(43.1)
30-32 weeks	70(50.3)
Birth weight (grams)	
< 1000 grams	37(26.6)
1000-2000 grams	102(73.3)
Weight percentile	
\leq 3%	44(31.6)
>3%	95(68.3)
Gender	
Male	70(50.3)
Female	69(49.7)
Source of admission	
Emergency room	73(52.5)
Labor room	66(47.5)
Outcome	
Discharged	133(95.6)
Died	6(4.3)

Table-I. Frequencies and percentages for socio-demographics

Complications	
Necrotizing enterocolitis (NEC)	3(2.1)
Mild Metabolic Acidosis	14(10)
Feeding intolerance	45(31.9)

Table-II. Frequencies of present complications

DISCUSSION

In this study, feeding intolerance was found to be the most common adverse effect. This finding is consistent with previous studies that have reported adverse effects of HMF on preterm neonates. In a study done in China by Zhang et al, done on 298 preterm infants showed feeding intolerance in 53.6%.⁶ In another study done in India in 2018, feeding intolerance was found in 14% of preterm.⁷ The higher incidence of this finding could possibly be due to high osmolality of feeds following fortification with HMF (464 mOsm/kg).⁸

In one study done in united stated in 2020 by Erika et al, showed metabolic acidosis in 34.4% while necrotizing enterocolitis in 2.4% cases close to our findings.⁹ Possible causes of metabolic acidosis with HMF could be improper mixing and amount of milk, though there is no direct impact of metabolic acidosis on neonatal growth and development, but this may add to feeding intolerance which can be easily overcome by properly diluting and mixing the milk with human milk fortifiers.

Although there is proven role of human milk fortifiers in weight gain of preterm and low birth weight infants¹⁰, significant adverse events like feeding intolerance, metabolic acidosis and necrotizing enterocolitis cannot be underestimated, though, with fortification occurring in the late feeding stage i.e., enteral volume if *80–100 mL/kg/day*, and slowing the time to reach complete fortification may minimize these effects.¹¹

The study has several limitations. Firstly, it is a descriptive study with a small sample size, which may limit the generalizability of the findings. Secondly, the study only observed the adverse effects of HMF without comparing them to a control group. Therefore, it is difficult to determine the direct causality between HMF and the observed complications.

CONCLUSION

This study provides insights into the adverse effects of Human Milk Fortifier on preterm neonates in a NICU setting. The findings suggest

that while HMF may enhance growth and improve certain outcomes in preterm infants, it is also associated with potential complications such as feeding intolerance, mild metabolic acidosis, and NEC. Healthcare professionals should carefully monitor preterm infants receiving HMF and consider the potential risks and benefits before prescribing it. Further research with larger sample sizes and controlled designs is needed to confirm these findings and explore strategies to minimize the adverse effects of HMF in preterm neonates.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.



Copyright© 25 July, 2024.

REFERENCES

1. **Preterm birth [Internet]**. Who.int. [cited 2021 Jun 8]. Available from: <https://www.who.int/news-room/fact-sheets/detail/preterm-birth>
2. Kousar T, Memon Y, Sheikh S, Memon S, Sehto R. **Risk factors and causes of death in Neonates**. Rawal Medical J. 2010; 35(2):205-8.
3. Eibensteiner F, Auer-Hackenberg L, Jilma B, Thanhaeuser M, Wald M, Haiden N. **Growth, feeding tolerance and metabolism in extreme preterm infants under an exclusive human milk diet**. Nutr. J. 2019 Jul; 11(7):1443.
4. Rochow N, Jochum F, Redlich A, Korinekova Z, Linnemann K, Weitmann K, et al. **Fortification of breast milk in VLBW infants: Metabolic acidosis is linked to the composition of fortifiers and alters weight gain and bone mineralization**. Clinical Nutrition. 2011 Feb 1; 30(1):99-105.
5. Arslanoglu S, Boquien CY, King C, Lamireau D, Tonetto P, Barnett D, et al. **Fortification of human milk for preterm infants: update and recommendations of the European Milk Bank Association (EMBA) Working Group on Human Milk Fortification**. Front Pediatr. 2019 Mar 22; 7:76.
6. Zhang T, Luo H, Wang H, Mu D. **Association of human milk fortifier and feeding intolerance in preterm infants: A cohort study about fortification strategies in Southwest China**. Nutr. J. 2022 Nov 2; 14(21):4610.

7. Pillai A, Albersheim S, Matheson J, Lalari V, Wei S, Innis SM, et al. **Evaluation of a concentrated preterm formula as a liquid human milk fortifier in preterm babies at increased risk of feed intolerance.** *Nutr. J.* 2018 Oct 4; 10(10):1433.
8. Siripattanapipong P, Yangthara B, Ngercham S. **Effect of fortifiers on the osmolality of preterm human milk.** *Paediatr Int Child Health.* 2019; volume (issue):1-4. doi: 10.1080/20469047.2019.1575537
9. Cordova EG, Soldateli B, Rosner B, Drouin K, Davitt E, Pepin HL, et al. **Growth and clinical outcomes of very low birth weight infants receiving acidified vs nonacidified liquid human milk fortifiers.** *Nutr Clin Pract.* 2021 Dec; 36(6):1304-11.
10. Kumar M, Upadhyay J, Basu S. **Fortification of human milk with infant formula for very low birth weight preterm infants: A systematic review.** *Indian Pediatr.* 2021 Mar; 58(issue#):253-8.
11. Lin R, Shen W, Wu F, Mao J, Liu L, Chang Y, et al. **Human milk fortification in very preterm infants in China: A Multicenter Survey.** *Front Pediatr.* 2022 Feb 23; 10:795222.

AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Hareem Syed	Idea conception, Review, Final review.	
2	Azeem Khan	Writeup, Final review.	
3	Faraz Ahmed	Review.	