

Case Report



Nutritional Management for Intolerance to Human Milk Fortifier in a Preterm Small-for-Gestational-Age Infant: a Case Report

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Conflict of Interest

The authors declare that they have no
competing interests.

ABSTRACT

Adequate nutrition is extremely crucial for the growth and development of preterm, small-for-gestational-age (SGA) infants owing to an increased risk of postnatal growth failure and poor neurodevelopmental outcome. Despite the beneficial properties of human milk (HM), it should be fortified to prevent extrauterine growth restriction; however, fortification of HM with a bovine-based human milk fortifier (BHMF) may induce feeding intolerance (FI) and necrotizing enterocolitis in preterm newborns. Herein, we have described the nutritional management of a preterm SGA newborn with intolerance to BHMF. A male infant was born at a gestational age of 32 weeks and 5 days, SGA weighing 1,490 grams (< 10th percentile). During BHMF use, he presented with symptoms of FI including abdominal distention, increased gastric residuals, and delayed enteral feeding advancement. Therefore, HM was fortified with carbohydrate powder, whey protein powder, and medium-chain triglycerides oil instead of BHMF to prevent FI and promote weight gain. Caloric density of feeds was increased once every 3 or 4 days by approximately 5 kcal/kg/day until an intake of 100 kcal/kg/day was achieved. Subsequently, his caloric and protein intake increased, growth rate improved, and full enteral feeding was achieved without any further symptom of FI. In conclusion, the symptoms of FI with BHMF in a preterm SGA neonate improved with the administration of a macronutrient fortified HM without compromising his enteral feed advancements, growth rate, and energy or protein intake.

Keywords: Feeding intolerance; Fortified food; Macronutrients; Premature infant; Small-for-gestational-age infant

INTRODUCTION

Postnatal growth failure remains an important clinical issue in preterm infants as they experience energy and nutrition deficits during the neonatal intensive care unit (NICU) hospitalization [1]. The growth outcomes in small-for-gestational-age (SGA) preterm neonates are markedly influenced jointly by prematurity and SGA status, resulting in growth restrictions in childhood [2]. Adequate nutritional support is essential for infants, especially in those born preterm and SGA with very low birth weight (VLBW), owing to a higher risk of postnatal growth failure and associated poor neurodevelopmental outcome [1].

Notwithstanding the high risks for feeding intolerance (FI) and necrotizing enterocolitis (NEC) in preterm infants, even the feeding guidelines for preterm SGA neonates are not well established and standardized, causing heterogeneity in enteral feeding practices among different neonatal units [3]. Nutrition support strategies to enhance the growth of preterm newborns include the provision of early enteral and parenteral nutrition, feeding human milk (HM), and fortified HM or using preterm formula (PM) in the absence of the mother's own milk and in case of enteral feeding volume advancements [4].

HM is known to be the best source of neonatal nutrition but considering the high nutritional requirements of preterm infants, it should be fortified to prevent extrauterine growth restriction and specific nutrient deficiencies [5]. However, fortification of HM with a bovine-based human milk fortifier (BHMF) has been reported to induce FI and NEC in preterm babies [6].

We aimed to share our clinical experience through this case report involving nutrition management in a preterm SGA newborn with FI to BHMF in the NICU setting. This case report was approved and the requirement for informed consent was waived by the Institutional Review Board of Hanyang University Hospital (2020-03-005). Electronic medical records were reviewed to collect data.

CASE

A male infant weighing 1,490 g (< 10th percentile) was delivered by cesarean section at 32 weeks and 5 days of gestation and was admitted to the NICU. Apgar scores at 1 and 5 min were 6 and 9, respectively. Parenteral nutrition (PN) with 10% dextrose (3.4–9 g/kg/day) and 20% SMOF lipid (0.7–3 g/kg/day; Fresenius Kabi, Austria) were initiated within an hour of NICU admission and were continued until the 7th day of life (DOL), and 10% PRIMENE amino acid solution (0.4–2 g/kg/day; Baxter Deutschland GMBH., Germany) was added 1 day after birth.

Trophic feeding (5 mL/kg/day) with HM or PM commenced on DOL 1 and was gradually advanced due to mild abdominal distention and increased gastric residuals from previous feedings. PN was gradually tapered off with the advancement in enteral feeding volumes and PN was discontinued on DOL 7 after a feeding volume of 80 mL/kg/day with HM was achieved; however, abdominal distention developed when enteral feeds with HM or PM reached 110 mL/kg/day, and therefore, feed volumes were reduced to half on DOL 10. Subsequently, he was fed solely with HM for the next 5 days and feedings were advanced in increments of 10–20 mL/kg/day.

Fortification of HM with powdered BHMF (Enfamil Human Milk Fortifier, Mead Johnson and Co., Evansville, IN, USA) at an enteral feeding volume of 110 mL/kg/day was started on DOL 15. HM (25 mL) was mixed with one packet of the fortifier (1.1 g protein/100 mL, 1 g lipids/100 mL, and 14 kcal energy/100 mL of HM) and administered; however, within 24 hours of BHMF administration, he developed glucose instability and lethargy. He was treated with amikacin and tazoperan (piperacillin, tazobactam) for suggested sepsis and enteral feeding volume was halved. As the infant's status stabilized, enteral feeding volumes were again advanced in an increment of 20–30 mL/kg/day. On DOL 17, enteral feeds were stopped and PN was administered because of suggested NEC with abdominal distention; however, on DOL 20, trophic feedings were restarted with HM or PM after a cross-table abdominal

X-ray and abdominal sonography showed no evidence of NEC. PN was discontinued, and a probiotic capsule (Lacidofil, Pharmbio Korea, Seoul, Korea) was administered after an episode of loose stools on DOL 25.

A second trial with BHMF was attempted on DOL 23 along with the advancement of feeds at a gradual increment of 10–20 mL/kg/day until the enteral feeding volumes reached 130 mL/kg/day on DOL 27. However, the feeds were poorly tolerated because of desaturation after feeding, increased respiratory rate and gastric residuals, and abdominal distention. Accordingly, feeding volume was reduced from 130 mL/kg/day to 90 mL/kg/day, treatment for suggested sepsis was initiated with tazoperan and amikacin, and the use of supplemental oxygen was performed on DOL 28. On DOL 29, enteral intake could not be advanced because of repeated bouts of abdominal distension.

Despite receiving half of the feed as a protein hydrolysate formula from DOL 30 onwards, he failed to reach feeding volumes of 120 mL/kg/day within 10 days because of a distended abdomen and increased gastric residuals, and particularly on DOL 34, a feed had to be omitted because of cloudy and bloody gastric residuals. Cerebrospinal fluid tap test was performed on DOL 34 but was not positive for the suggested sepsis. Intravenous glucose and amino acid solutions were administered to improve glycemic control and for weight gain from DOL 38 to DOL 41; however, owing to low blood urea nitrogen levels (< 9 mg/dL) and repeated hypoglycemic episodes, he was weaned back to PM on DOL 41 for the next 2 days.

Considering his poor weight gain status since birth and insufficient feeding volume, HM was fortified with additional carbohydrate powder (HiCAL; Korea Medical Foods), whey protein powder (CareWell PRO; Korea Enteral Foods), and medium-chain triglycerides oil (Medifood MCT Oil; Korea Medical Foods) to increase caloric density to about 85 kcal/kg/d (additional 2 g protein/100 mL, 0.5 g lipids/100 mL, and 1.5 g carbohydrate/100 mL of HM; Level 1) on DOL 43. He was fed exclusively with HM fortified with macronutrients, and caloric density of feeds was increased once every 3 or 4 days by approximately 5 kcal/kg/day if tolerated until an intake of about 100 kcal/kg/day (Level 4) was achieved to meet the patient's estimated caloric goal of 120 kcal/kg/day. **Table 1** shows the nutrient content of BHMF fortified HM and macronutrients fortified HM according to the level of fortification. The fortification recipe was designed to achieve 30 to 60% energy from fat, and 2.8 to 4.0 g protein/kg/day to avoid undesirable carbon dioxide production, improve nitrogen retention or weight gain, and maintain an osmolality not exceeding 450 mOsm/kg [7]. The average estimated osmolality of macronutrients fortified HM was 372 mOsm/kg based on the prediction equation [8]. The infant remained stable on the feeds for 14 days and gained 18 g/day in comparison to 11 g/day before the fortification of HM with macronutrients, even after considering nil per os (NPO) status before and after inguinal hernia repair on DOL 48. Parenteral glucose and amino acid solutions were administered from DOL 47 to DOL 52.

Table 1. Nutrient content in BHMF fortified HM and macronutrients fortified HM

Nutrients (/100 mL)	BHMF fortified HM	Macronutrients fortified HM			
		1*	2*	3*	4*
Energy (kcal)	81.0	84.3	88.3	95.1	99.4
Protein (g)	2.5	3.3	3.3	2.3	2.3
Carbohydrate (g)	< 7.0	8.1	9.1	10.6	10.6
Fat (g)	4.9	4.4	4.4	4.9	5.4

BHMF, bovine-based human milk fortifier; HM, human milk.

*The number refers to the fortification level of macronutrients fortified HM, and the higher number indicates higher caloric density.

Table 2. Changes in mean nutrient intake, feeding volume, and growth rate before and during the use of macronutrients fortified HM

Variables	Before fortification*	During fortification†
Caloric intake (kcal/kg/day)	83	105
Protein intake (g/kg/day)	2.3	3.0
Feeding volume (mL/kg/day)	81	97
Growth rate (g/day)	11	18

HM, human milk.

*Refers to the period from initiation of trophic feeding to a day before the first day of administration of macronutrients fortified HM. †Refers to the period from initiation of macronutrients fortified HM to a day before discharge.

Enteral feeding volume was gradually advanced following surgery for the next 7 days, and it reached 140 ml/kg/day on DOL 55. Calorie and protein intake were also increased from 83 kcal/kg/day and 2.3 g/kg/day to 105 kcal/kg/day and 3.0 g/kg/day, respectively, with macronutrients fortification (**Table 2**). Before discharge, the infant neither had abdominal distention nor had other symptoms of FI. His enteral feeding volume had reached 140 mL/kg, and his calorie intake was 139 kcal/kg/day. His serum calcium, phosphorous and alkaline phosphatase levels were within the normal range for preterm infants at 10.9 mg/dL, 4.1 mg/dL, and 423 U/L, respectively.

DISCUSSION

We reported a case concerning nutrition management in a preterm SGA infant demonstrating FI with powdered BHMF. The neonate presented with a delayed time to achieve full enteral feeding, increased gastric residuals, and abdominal distention in multiple trials of BHMF administration. HM fortified with macronutrients ameliorated the newborn's FI symptoms and provided a good, *albeit* a short-term nutritional outcome such as increased caloric and protein intake, improved growth, and the achievement of full enteral feeding.

Adequate nutrition is essential for the growth and healthy development of preterm SGA newborns [1]. HM is the best form of nutrition for infants; however, premature infants need fortified HM to meet the high energy and nutrient requirements. Various products depending on the milk source and nutrient composition are available for fortifying HM [5]. Most of the commercially available multi-nutrient fortified HM brands contain bovine milk, and this case described the FI to bovine-based multi-nutrient fortified HM in a preterm baby [6].

FI resulting from the administration of multi-nutrient BHMF in premature newborns is probably related to the high osmolarity of the feeds and bovine-milk derived protein. It has been suggested that multi-nutrient fortified HM with an increased osmolarity over the recommended upper limit of 400 mOsm/L (approximately an osmolality of 450 mOsm/kg) could lead to FI by causing interference with gastric emptying [9]. Furthermore, the differences in protein composition of HM and bovine milk resulting in a slower gastric emptying rate and decreased protein digestibility in newborns could be responsible for FI [10].

Interestingly, bovine-based whey protein powder used in the fortification of HM in this study did not cause any FI in the preterm SGA neonate. BHMF contains a casein-predominant bovine-milk protein isolate that is different from the casein composition in HM [11], whereas the whey protein powder contains only bovine whey proteins such as α -lactalbumin, β -lactoglobulin, lactoferrin, lactoperoxidase, and bovine serum albumin. It has been

suggested that whey-dominant formula might contribute to an increased gastric emptying rate by forming a finer and softer curd than the casein-dominant formula in newborns, thus allowing easy digestion [11]. Furthermore, powdered carbohydrate supplement used in this study contained soluble fiber from chicory, which may have a prebiotic effect in newborns [12]. In the randomized controlled trial in VLBW infants [13], Dilli et al. reported that probiotics and synbiotics could decrease NEC but not prebiotics alone. It is also possible that inulin from chicory in the carbohydrate supplement used in our study acted synergistically as a substrate for the administered probiotics resulting in beneficial effects on FI.

Administration of HM fortified with macronutrients resulted in an increased caloric and protein intake, improved growth rate, and achievement of full enteral feeding in our study. Morlacchi et al. [14] also showed that fortifying HM individually with macronutrients based on its protein, fat, and carbohydrate content promoted growth in VLBW preterm infants without any sign of gastrointestinal or metabolic intolerance; however, in this study, calculated levels of macronutrients were added to HM on the basis of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition recommendations [15]. The mean values for protein, carbohydrates, and fat content in fortified HM used in our study were 3 g/kg/day, 9.5 g/kg/day, and 4.8 g/kg/day, respectively, and were lesser than the recommendations. It should be noted that during the period of macronutrient fortification of HM, enteral feeding volumes in the newborn had been reduced to NPO status with regards to inguinal hernia repair, and the infant achieved full enteral feeds within a week after the operation without any GI symptom. Thus, if it were not for surgery, the macronutrients content in fortified HM would have met the nutrient requirements.

To the best of our knowledge, this is the first case report suggesting fortification of HM with macronutrients as a feeding approach for preterm SGA infants with FI to BHMF. However, the study is limited by its descriptive and retrospective nature. Moreover, there is insufficient evidence regarding the effects of macronutrients supplementation of HM on safety, long-term growth, body fat, obesity, heart problems, high blood sugar, and brain development in preterm SGA newborns. Therefore, the results of this case report should not be generalized to the population at large but rather could be used as a basis for further study in the field.

In conclusion, FI to BHMF in a SGA preterm neonate improved with macronutrient fortified of HM without compromising on his enteral feeding progression, growth rate, and energy or protein intake. Further research is needed to confirm whether macronutrients fortified HM improve FI and determine the long-term consequences of such treatments in preterm SGA infants in larger properly designed randomized controlled studies.

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