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Original Article

Investigation of the effect of early and late breast milk enrichment on growth parameters in preterm infants: A randomized clinical trial

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Abstract

Background and aims: This study aimed to investigate and compare the effect of early and late breast milk fortification on growth parameters in preterm infants.

Methods: In this clinical trial, 90 preterm infants (28-32 weeks) admitted to the neonatal intensive care unit (NICU) of Hajar Hospital in Shahrekord, Iran were randomly divided into three groups. The fortification was performed when the milk intake reached 30 (group A), 70 (group B), and 100 cc/kg (group C). The height, weight, and head circumference of newborns were measured at the beginning of birth and 4 weeks after the birth. The incidence of sepsis and necrotizing enterocolitis, and milk tolerance were investigated as well. All analyses were conducted with Stata software, and *P* values <0.05 were considered statistically significant.

Results: The value changes in the height, weight, and head circumference in all three groups at 4 weeks were significant ($P<0.001$). The mean weight changes in the A, B, and C groups were 727.33 ± 163.85, 947.33 ± 155.38, and 808.66 ± 168.82, indicating a statistically significant difference ($P<0.001$). Further, the mean change of weight after 4 weeks showed statistically significant differences ($P<0.001$) among the A, B, and C groups. The weight gain in the B group was significantly higher than that of the A and C groups ($P<0.05$); however, no significant difference was observed in the mean weight gain between the A and C groups ($P=0.264$).

Conclusion: The breast milk fortification when the milk intake reached 70 cc/kg had better efficiency on neonatal weight gain compared with the early and delayed fortification.

Keywords: Preterm infant, Colostrum, Milk fortifier

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Introduction

Low weight at birth and premature birth as major health issues are the most important causes of neonatal mortality in developing countries (1). According to the conducted studies, 11% of all deliveries lead to premature birth, and 75%-80% of neonatal mortality and morbidity are due to premature birth (before 37 weeks) (2). Approximately 1900 infant deaths occur each year in Iran due to complications such as premature birth, weight gain, and the like. The prevalence of low birth weight in Iran, according to the latest statistics, is 9.6%-11.8% (3). The immature function of various organs of the premature infant, treatment complications, and special disorders that cause premature labor increase the risk of various diseases and the risk of the death of low birth weight infants compared to normal infants (4). These infants are in danger of many complications, including respiratory distress syndrome, chronic lung disease, intracerebral hemorrhage, long-term mental and neurological complications, necrotizing enterocolitis, and sensory-neural development disorder (5). In recent years, with the advancement in prenatal care and the establishment of the neonatal intensive care unit (NICU), the survival rate of preterm, low, and very low birth weight infants has increased significantly, but the increase in the survival of these infants has not been accompanied by a reduction in low birth weight complications. Moreover, the surviving infants are more likely in danger of problems such as severe disabilities, mental retardation, cerebral palsy, and vision and hearing problems (6-8). Breast milk is not alone able to meet the nutritional needs of low birth weight infants (9). The composition of breast milk changes over time. For example, in preterm mothers, the amount of protein in breast milk is higher than that in the first weeks of breastfeeding, and this amount represents a gradual decrease (10). In addition, milk production in the mothers of preterm infants is affected by various factors such as stress, illness, delayed breastfeeding, and distance from the baby. Therefore, breast milk cannot meet the nutritional needs of the baby, and the use of breast milk alone causes developmental disorders in infants. Inadequate weight gain can lead to developmental disorders and neurological

complications, including hearing, vision, and mental retardation in the baby (11). Therefore, commercial breastfeeding enrichments have been developed and are widely used in NICUs to prevent these side effects, as well as to benefit from breast milk (12). It has been observed that the use of breast milk enrichers and improves the growth and sensory-motor development of infants in the future (13). There are currently several ways to use these enrichers. One of these methods is to use a constant amount of enrichment during the required period, which does not take into account changes in the composition of breast milk over time; some patients receive more, while some others receive less than the required amount of food. The next method is called the regulatory method, in which the amount of enrichment needed by the baby is calculated based on the level of serum blood urea nitrogen as a measure of protein intake. The disadvantages of this method include the disproportionate estimation of the baby's needs. Another method, which is the gold standard, is called the targeted method, in which breast milk is analyzed spectroscopically and to which enrichers are added according to the need for enrichment (14). There is currently no consensus on when to start these enrichments, and the US and European guidelines have provided different numbers based on the studies of their populations that are likely to be inconsistent with the Iranian population. Therefore, this study was designed to examine and compare different values and determine the best time to start enrichment.

Methods

The present clinical trial was performed on premature infants admitted to the NICU of Hajar Hospital in Shahrekord, Iran in 2018. The inclusion criteria included premature infants (28-32 weeks weighing less than 2000 g) and legal guardian consent for the infant to participate in the study. On the other hand, the exclusion criteria were any congenital anomalies, feeding with formula, prohibition of using breast milk, and the dissatisfaction of legal guardians during the study.

A sample volume of 27 individuals was obtained for each group based on a previous study that reported a weighted index of 1290±307 g before the intervention and 1590±399 g after the intervention with fortified milk (15), as well as a 95% confidence level and a formula used for calculating the sample volume with alpha = 0.05, ma1 = 1290, power = 0.85, ma2 = 1590. To increase the precision in each group, the sample size was 30 people. The sampling method was a census of premature infants admitted to the ICU of Hajar Hospital, Shahrekord, Iran, and then the neonates were randomly divided into 3 groups using randomization performed with random allocation software and random blocking. The flow diagram of the randomized clinical trial (RCT), with was one-sided blinding, is depicted in Figure 1. The parents of the participants were unaware of being in the groups. On the first day of lactation, infants weighing less than 1000 g were fed with 0.5-1 cc/kg of milk each hour by gavage. Infants weighing 1000-1500 g were fed with 2-3 cc/kg by gavage every two hours, and infants weighing more than 1600 g were fed every 2-3 hours with more tolerable volume and by gavage. After the first day, the amount of milk was 10-20 cc/kg/d and increased to a maximum of 180-200 cc/kg/d within the tolerance of the infant. The fortification was performed when the milk intake reached 30 (group A), 70 (group B), and 100 cc/kg (group C). To enrich breast milk, 4.4 g of Aptamil supplement (FMS fortified milk) was dissolved in 100 cc of breast milk and then fed to the infant. Each 4.4 g Aptamil supplement (FMS fortified milk) contains 1.1 g protein, 0 g fat, 2.7 g carbohydrate, 35 mg sodium, 23 mg potassium, 25 mg chlorine, 5 mg magnesium, 38 mg phosphorus, 66 mg calcium, 610 µg zinc, 232 units' vitamin A, 200 units' vitamin D, 6.4 µg vitamin K, 132 µg vitamin B-12, 173 µg of vitamin B-2, and 2.6 mg of niacin (12). The height, weight, and head circumference of the newborns were measured at the beginning of birth and 4 weeks after the birth and recorded in a related checklist. The incidence of sepsis and necrotizing enterocolitis, and milk tolerance were evaluated as well. Descriptive and analytical statistics, including frequency percentage (%) and mean [±standard deviation (SD)], were used for data analysis. In addition, paired t- and one-way analysis of variance (ANOVA) tests were used to compare the mean value in each group and three groups, respectively. All analyses were conducted with Stata software, and P values < 0.05 were considered statistically significant.

Results

Tables 1 and 2 present the results of the mean height, weight, and head circumference of infants at birth and 4 weeks after birth in the study groups. According to the results of ANOVA, the mean height, weight, and head circumference among the three groups were not significant after 4 weeks of intervention. A comparison of height, weight, and head circumference before (at birth) and after (4 weeks after birth) intervention in each group is reported in Table 3. Based on ANOVA results, the mean changes in the height and head circumference among the study groups demonstrated no significant difference ($P > 0.05$). However, the mean weight changes in the A, B, and C groups were 727.33±163.85, 947.33±155.38 g, and 808.66±168.82, indicating a significant difference ($P < 0.001$). According to the obtained data, the mean weight gain in the B group was significantly higher than that of the A and C groups ($P < 0.05$), but the mean weight gain between the A and C groups was not significantly different ($P > 0.05$).

Between comparisons mean changes in the height, weight, and head circumference of neonates after 4 weeks in the study groups are provided in Table 4.

Discussion

The present study evaluated 90 preterm infants admitted

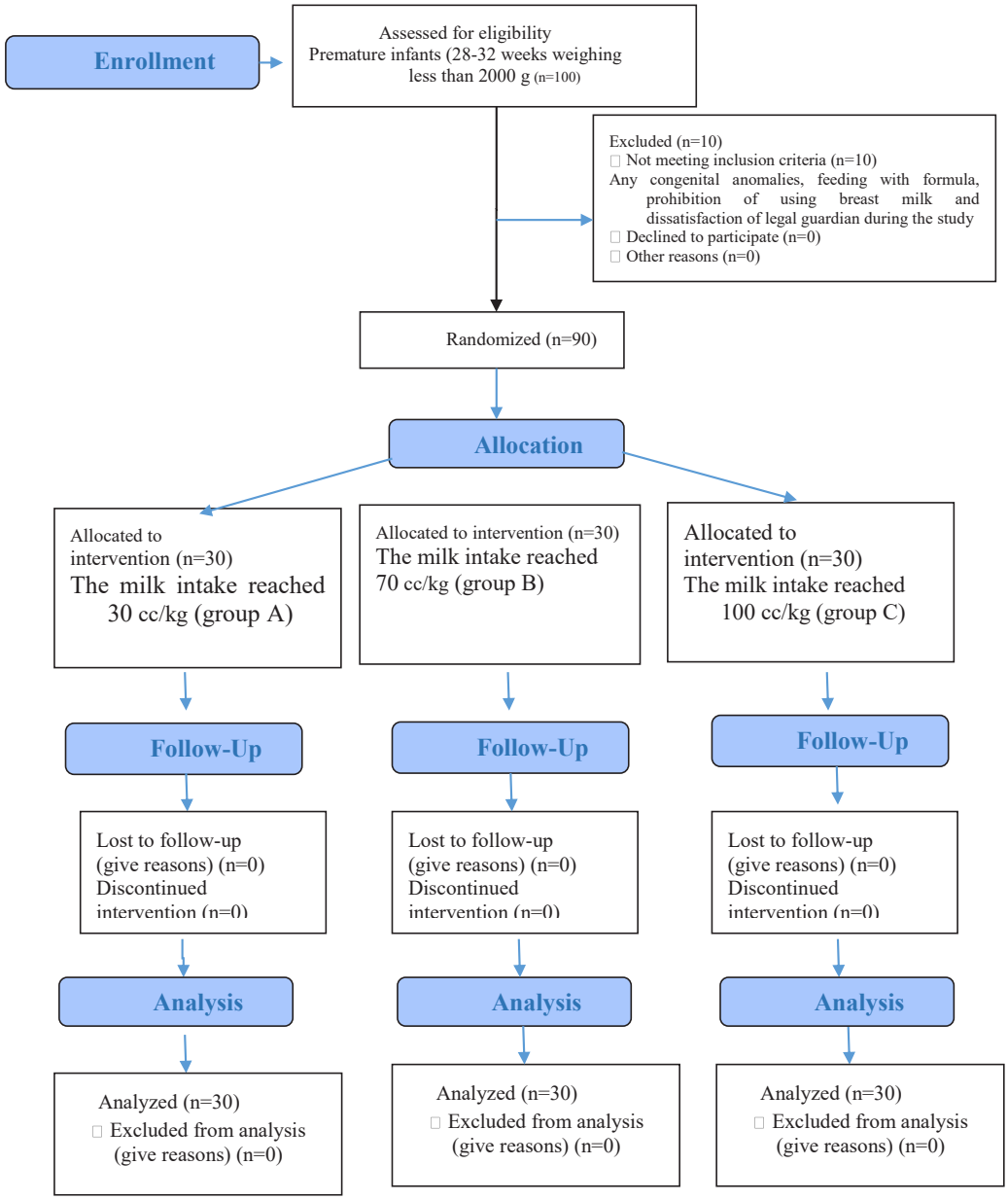

Figure 1. Flow Diagram for the investigation and comparison of the effect of early and late breast milk enrichment on preterm infants.

to the ICU of Hajar Hospital, Shahrekord, Iran in three groups (enrichment after reaching milk intake of 30, 70, and 100 cc/kg). Mean height, weight, and head circumference increased significantly after 4 weeks of birth in all three groups ($P < 0.05$). Although the mean changes in height and head circumference were not significantly different among the study groups ($P > 0.05$), the mean weight gain in the second group was significantly higher than that of the other groups ($P < 0.05$). Necrotizing enterocolitis, milk tolerance, and sepsis were observed in none of the infants in the studied groups.

Similar and occasionally contradictory results have been reported in studies conducted in this regard. In a study by Schulz et al, quick (starting at 20 mL/kg/d) and delayed (starting at 100 mL/kg/d) enrichment of breast milk in very low birth weight infants were investigated, and it was found that nutritional tolerance, enterocolitis necrosis, weight gain, duration of parenteral nutrition, and duration of hospital stay did not significantly differ between the two groups (16). In the study of Taheri et al, the increase in height, weight, and head circumference, as well as the incidence of malnutrition, necrotizing enterocolitis, and sepsis, demonstrated no significant difference between the two groups of quick (starting from 20 mL/kg/d) and delayed (starting from 70 mL/kg/d) enrichment (15). In the study by Sajjadian et al, the rate of weight gain, the incidence of sepsis, osteopenia, tolerance, and necrotic enterocolitis were not significantly different between the two groups of quick and delayed enrichment; therefore, the researchers suggested that delayed enrichment is more economical and should be used accordingly (17). In the study by Tillman et al, 53 preterm infants were studied in early (from the first day of feeding) and delayed (when feeding reached 50-80 mL/kg/d) enrichment groups. The researchers observed no significant difference in the weight of infants (at week

Table 1. Descriptive of height, weight, and head circumference at birth among groups and comparison

Variable	Group	Min.	Max.	Mean ± SD	*P* value
Height (cm)	1	35.0	44.0	40.433 ± 2.7628	0.898
	2	32.0	47.0	40.267 ± 3.6097	
	3	33.0	44.0	40.067 ± 2.7283	
	Total	32.0	47.0	40.256 ± 3.0300	
Weight (g)	1	940.0	2100	1645.000 ±305.20	0.155
	2	990.0	2000	1517.667 ± 248.20	
	3	950.0	2000	1518.000 ± 315.46	
	Total	940.0	2100	1560.222 ± 294.08	
Head circumference (cm)	1	26.0	33.0	29.967 ± 1.4499	0.350
	2	26.0	32.0	29.500 ± 1.6348	
	3	26.0	33.0	29.350 ± 1.9963	
	Total	26.0	33.0	29.606 ± 1.7100	

Note. Min.: Minimum; Max.: Maximum; SD: Standard deviation.

Table 2. Comparison of height, weight, and head circumference between groups after intervention (4 weeks after birth)

Variable	Group	Mean ± SD	*P* value
Height (cm)	1	45.8 ± 2.6	0.3175
	2	45.5 ± 3.7	
	3	44.6 ± 3.1	
	Total	45.3 ± 3.1	
Weight (g)	1	2372 ± 297	0.2749
	2	2465 ± 283	
	3	2326 ± 44	
	Total	2388 ± 338	
Head circumference (cm)	1	33.1 ± 2.3	0.378
	2	33.2 ± 1.9	
	3	43.1 ± 5.0	
	Total	36.4 ± 31.0	

Note. SD: Standard deviation.

34 of PMA) and the consequences, including nutrition intolerance and necrotizing enterocolitis between the two groups (18). Sullivan et al studied preterm infants in early (starting from 40 mL/kg/d) and delayed (starting from 100 mL/kg/d) enrichment groups and found no differences in the growth, intolerance nutrition, and the incidence of enterocolitis necrosis between the two groups (9). In another study by Shah et al, 100 premature infants were divided into early (starting from milk intake of 20 cc/kg/d) and late (starting from milk intake of 100 cc/kg/d) enrichment groups. Their results revealed that the nutritional tolerance and incidence of necrotizing enterocolitis did not differ significantly between the two groups, but protein intake in the early enrichment group in the first, second, and third weeks was higher than that of the delayed enrichment group (19).

Although the results of studies indicated that early and delayed enrichment did not have a significant effect on embryonic development and outcomes, in the present study, it was observed that weight gain in the enrichment group started from milk intake of 70 cc/kg/d had the highest rate. In a systematic review, Mimouni et al evaluated RCTs comparing the effectiveness of the early and delayed enrichment of breast milk on growth and major outcomes and concluded that there was little evidence of better efficacy of early enrichment. Thus, they suggested that delayed enrichment seems to be more cost-effective. However, it is recommended that other studies evaluate the effectiveness of early and delayed enrichment over a longer period on significant growth and outcomes (20).

One of the limitations of previous studies and the present study is the lack of measurement of the protein and caloric content of breast milk in different groups because the difference in the protein content and breast milk in different groups may affect the final results. In this regard, Rochow et al reported that the calorie and protein content of the breast milk of different mothers may represent significant differences (12).

In general, the results of the present study demonstrated that breast milk enrichment from milk intake of 70 cc/kg/d was more effective than early (starting from milk intake of 20 cc/kg/d) and delayed (starting from milk intake of 100 cc/kg/d) enrichment on neonatal weight gain. However, the incidence of nutritional tolerance, sepsis, and necrotizing enterocolitis show significant differences among the studied groups. Given that there is little evidence to support the findings of the present study, it is recommended that in future studies, infants be followed for a longer period in terms of weight gain and important outcomes.

Conclusion

The results of the current study revealed that breast milk enrichment starting from milk intake of 70 cc/kg/d is more effective than early (starting from milk intake of 20 cc/kg/d) and delayed (starting from milk intake of 100 cc/kg/d) enrichment on neonatal weight gain. In addition, in the present study, no significant differences were observed in important outcomes such as necrotizing enterocolitis, sepsis, and nutritional tolerance among the studied groups. Therefore, breast milk enrichment starting from

Table 3. Comparison of height, weight, and head circumference before (at birth) and after (4 weeks after birth) intervention in each group

Variable		Before intervention (Mean ± SD)	After intervention (Mean ± SD)	*P* value (Paired *t* test)
Group A	Height (cm)	40.43±2.76	45.81±2.64	<0.001
	Weight (g)	1645.00±305.20	2372.33±297.63	<0.001
	Head circumference (cm)	29.96±1.44	33.10±2.33	<0.001
Group B	Height (cm)	40.41±3.58	45.55±3.72	<0.001
	Weight (g)	1517.66±248.20	2465.00±283.80	<0.001
	Head circumference (cm)	29.50±1.63	33.26±1.91	<0.001
Group C	Height (cm)	40.06±2.27	44.63±3.01	<0.001
	Weight (g)	1518.00±315.45	2326.66±414.75	<0.001
	Head circumference (cm)	29.35±1.99	43.01±54.25	0.181

Note. SD: Standard deviation.

Table 4. Between comparisons mean changes in the height, weight, and head circumference of neonates after 4 weeks in the study groups

Variable		Changes (Mean ± SD)	*P* value
Height (cm)	Group A	5.38±0.99	0.066
	Group B	5.13±1.42	
	Group C	4.56±1.62	
	Total	5.02±1.39	
Weight (g)	Group A	727.33±163.85	<0.001
	Group B	947.33±155.38	
	Group C	808.66±168.82	
	Total	827.77±185.05	
Head circumference (cm)	Group A	3.13±1.70	0.354
	Group B	3.76±0.79	
	Group C	13.66±54.65	
	Total	6.85±31.59	

Note. SD: Standard deviation.

a milk intake of 70 cc/kg/d, in addition to improving the weight of the baby, can be considered more economical.

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Authors' Contribution

MH and NA conceived and design the study. MH, NA, and RC supervised intervention sessions and data collection. RC participated in the analysis and carried out the data. MH, NA wrote the first draft of the manuscript. All authors contributed to the writing of the paper, and read and approved the final manuscript.

Conflict of Interests

The authors declare that there is no conflict of interest.

Ethical Approval

The study protocol was registered by the Iranian Registry of Clinical Trials (identifier: IRCT20171030037093N3). This study was conducted following the principles of the Declaration of Helsinki and then its protocol was approved by the Ethics Committee of Shahrekord University of Medical Sciences (IR.SKUMS.REC.1397.145).

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