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Effect of Fortification of Breast Milk in Conjugation with Protein Supplement on Neurodevelopment of Preterm Low Birth Weight Infants at 3 Years

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ABSTRACT

Introduction: Choice of appropriate nutrition has a special place, which variations in dietary nutrient can potentially be involved in growth deficits in preterm neonates. **Aim:** to investigate the effect of protein supplementation in very low birth weight (VLBW= birth weight under 1500 grams) infants on neurological growth in the third year of birth. **Material and Methods:** We investigated neurological growth in two groups of control and intervention (each group, n= 18 subjects). The intervention group includes 3-year-old children who weighting less than 1200 grams at birth and have received protein supplementation at the course of NICU hospitalization, protein was added to maternal milk when the amount of milk reaches to 100 cc/kg/day, at this time parenteral nutrition was discontinued and the volume of feeding was increased 20cc/kg/day until reached to 150-180cc/kg/day. We also added the fortifier to breast milk at this time (FMS- Aptamil- DANON). The fortification and the protein supplementation were stopped when the weight of the baby reached to 1500 grams. The control group was fed similar to the intervention group, without protein supplemental intake. Neurodevelopmental outcomes were evaluated using ASQ, NEWSHA and BINS tools. **Results:** There was no significant difference between the mean head circumference in the two groups (p=0.209). There was no significant relationship between neurological growth rate evaluated by BINS tool in two groups (p=0.266). There was a significant correlation between the neurological development assessed by the ASQ tool in the areas of communication (p=0.014) and gross motor (p=0.001) in the two groups, however, no significant relationship was found in terms of fine motor (p=0.63), problem solving (p=0.07) and personal-social relationships in both groups (p=0.152). There was a significant correlation between neurological development evaluated using the NEWSHA tool in terms of auditory (p=0.031), verbal language (p=0.024), cognitive (p=0.007), social connection (p=0.034) and motor (p=0.002) in the two groups. **Conclusion:** Protein intake in preterm infants didn't reveal long term effects on the growth of head circumference. Moreover, it was capable of improving neurological growth in the areas of communication and gross motor (based on the ASQ) and auditory, verbal language, cognitive, social connection, and motor (based on the NEWSHA).

Keywords: Preterm infants, Extremely low birth weight, Protein intake, Neurological development.

1. INTRODUCTION

Preterm birth is referred to a birth that happens at fewer than 37 weeks of gestational age. According to the WHO, the prevalence of premature birth is increasing in most countries over the past decades (1).

Of the 121 million neonates born in the world every year, approximately 23 million low-birth weight babies (weighing less than 2500 grams) are born, the majority of which is related to developing countries (2-3). Preterm births are considered to be the leading cause of death in infant under the age of 5 years all over the word in 2016, accounting for 16% of total death and 35% of infant deaths (5). It is noteworthy that preterm birth can be linked to short-term and long-term complications, leading to remarkable costs to health systems as well as financial and psychological problems to families (6-9). Late preterm birth (34<37 weeks) is usually found to be associated with an increased risks of adverse outcomes, while comparing with term birth (8, 10)

The development of neonatal intensive care technology has led to a reduction in premature infants, but it does not affect the prevalence of adverse developmental disabilities and long-term complications in preterm infant who survive (11, 12). Ample evidence suggests that bright and high sound levels is considered to adversely interfere with the development of the preterm infants in neonatal intensive care unit (NICU (13, 14).

The effect of developmental care on outcomes of preterm neonates has been indicated to be mix; however better outcomes have been previously indicated (11, 15, 16). On the other hand, recent studies suggest that NICU has a negative effect on the growth of high risk neonates with vulnerable brain; even treatment with oxygen and steroids has short-term positive and long-term negative effects on these babies (17, 18).

Overall, the current evidence indicated NICU environment is associated with neurodevelopmental outcome, where a strong association of room type with brain activity and brain structure with neurodevelopmental outcome has been reported in the prematurely-born neonates (11). Therefore, the success in increasing the survival rate of low-birth-weight and preterm infants poses the issue of the future development of this vulnerable group (19, 20). Accumulating body of evidence suggests the association of early nutrition with growth, and neurodevelopment in extremely low birth weight (ELBW) neonates (21-23). Furthermore, it has been indicated that improvement in growth parameters can be observed by administering a nutrient-enriched diet, but neurodevelopmental outcomes can be affected by this kind of supplementation (24, 25). However, choice of appropriate nutrition has been revealed to be of great importance, where variations in dietary nutrient were found to lead to growth deficits in preterm neonates (26, 27).

The impact of breastfeeding on the health and growth of preterm infants is undeniable. Feeding mother's milk has been indicated to play a key role in improving child neurodevelopment in ELBW neonate (<1500 g) (23, 28).

Nevertheless, VLBW infants need human milk supplementation because of their physiological properties (i.e., poor sucking and swallowing reflexes), (29-31). The short-term prognosis and association of childhood nutrition is with diseases of adulthood can explain supplementation for providing adequate quality amino acids and fatty acids (31-33). Growth failure is a common problem in VLBW fed exclusively with breast milk (34-36). Furthermore, mother milk alone is not sufficient to adequately provide the preterm babies' needs of minerals, vitamins, proteins, etc. (37). Feeding human milk alone has been indicated to be involved in decreasing growth and lower increase in head circumference in preterm infants than feeding these infants with fortified human milk (38). Recent evidence suggests that nutrition of premature infants with protein-rich diets is associated with a positive nitrogen balance, enhanced protein synthesis in the body, improved postnatal growth, improved cognitive function, and progress in brain construction (36).

It has been reported that fortification with proteins can be capable of enhancing the weight gain, head growth and linear growth in preterm babies, but protein-alone fortification has been not demonstrated to be linked to neurological development and long-term growth (39, 40). The benefits of monocomponent fortification with carbohydrates and fats are currently debatable, where there is no ample evidence supporting this issue. However, further studies are currently needed to provide ample evidence for supplementation with proteins or other nutrients affecting neurological development.

2. AIM

Nevertheless, the aim of this study was to investigate the effect of protein supplementation in ELBW infants on neurological growth in the third year of birth. This study was an RCT (was registered in IRCT) that designed to investigate the growth of newborns following supplemental protein used and the results was mentioned in the previous article (41) and after three years we designed present study to evaluate the nourological outcome of that babies.

3. MATERIAL AND METHODS

This study was approved by Research Ethics Committee of the Iran University of the Medical Science, protocol number IR.IUMS.FMD.RED.REC1396.8911215336. Procedures were conducted in accordance with the Declaration of Helsinki for human studies of the World Medical Association.

This clinical trial study was performed on babies weighing less than 1200 grams, who were admitted to the NICU of Akbar Abadi Hospital in Tehran, Iran during 2014-2015. The intervention group includes 3-year-old children who weighting less than 1200 grams at birth and has received protein supplementation at the course of NICU hospitalization, we started enteral nutrition after 48 hours from birth as minimal enteral feeding and the volume of feeding was increased 20cc/kg/day. Protein was added to maternal milk when the amount of milk reaches to 100 cc/kg/day, at this time parenteral nutrition was discontinued and the volume of feeding was increased 20cc/kg/day until reached to 150-180cc/kg/day. We also added the fortifier to breast milk at this time (FMS, Aptamil, DANON, and Netherlands). The fortification and the protein supplementation were stopped when the weight of the baby reached to 1500 grams. The control group was fed similar to the intervention group, without protein supplemental intake. This study was designed to investigate the growth of newborns following supplemental protein used and the results were mentioned in the previous article (41). A group of these children were breastfed with mother milk in conjunction with human milk fortifier, and protein (18 subjects). Furthermore, other group received mother milk and human milk fortifier, which these infants have reached the age of 3 (18 subjects). Unfortunately, we encountered a drop in the number of subjects (e.g., lack of access to infants, mistakes in call numbers, etc.). Therefore, 18 infants in each group were randomly enrolled in the present study.

In the first group (intervention), neonates at first week of their life received a protein powder supplement of 0.8-0.6 grams per day which added to maternal milk in two or three separated dose, and the volume intake of breast milk (200-100 cc/kg of infant weight per day) was similar

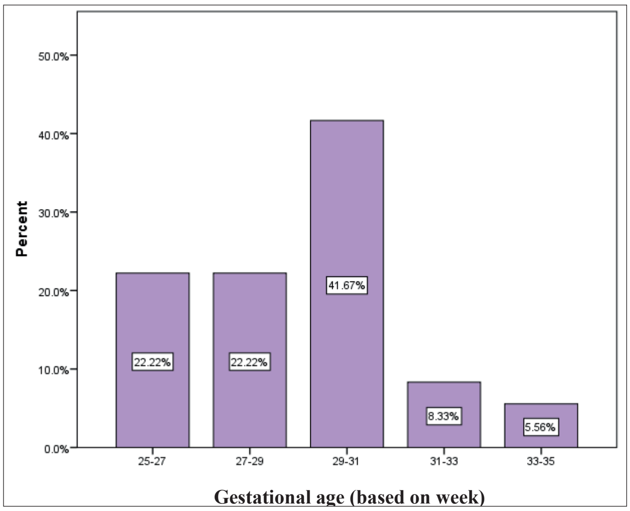

Figure 1. Distribution of gestational age in newborns

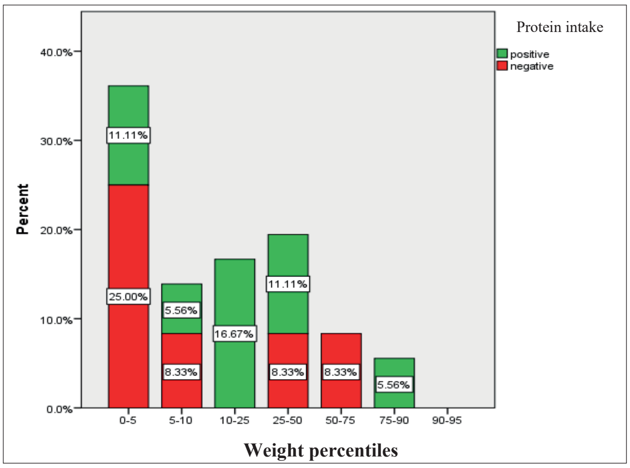

Figure 2. Distribution of current weight in patients

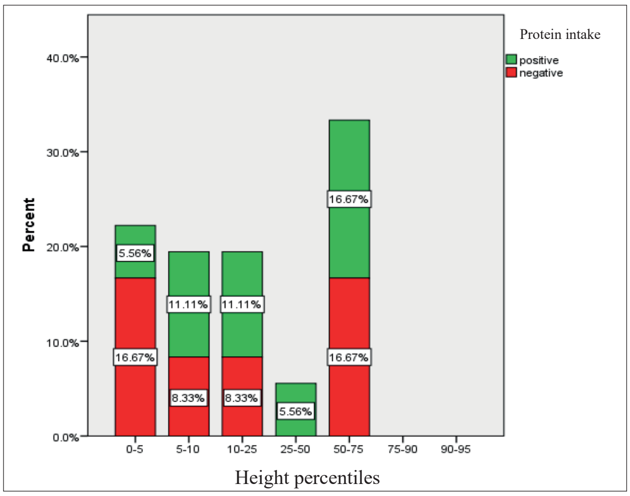

Figure 3. Distribution of current stature in patients

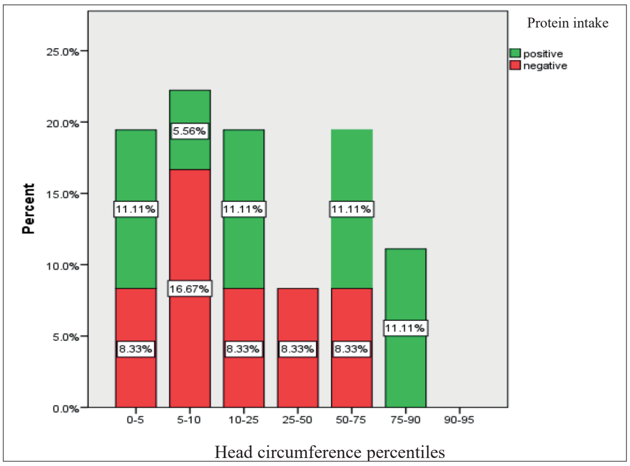

Figure 4. Distribution of current head circumference in patients. Positive= received protein supplement, Negative= without protein supplement

in two groups. The complementary protein was the same in all infants of the intervention group. The brand name is not mentioned in the present study due to the advertising aspect.

The contact was made with the families of the newborns by phone and the necessary coordination was done for their presence in a day's clinic in Akbar Abadi Hospital. On a specified day, all infants were examined by a therapist at the clinic and their neurological growth was measured using bins, asq, newsha tools. The therapist involved in recruitment and evaluation was blinded to the intervention allocation (fortification with or without protein) via the study.

The Ages and Stages Questionnaire (ASQ) was used in the study for evaluating skills of infants from 2 to 60 months, which is useful tool to determine infant at risk for developmental delay.

This questionnaire is consisted of 30 parent-completed questions that are capable of screening the developmental performance in five categories (gross and fine motor skills, communication, solving the difficulties, and personal- social interaction). It is noteworthy that 15 to 20 minutes are required to complete the questionnaire by parents or other caregivers, and 2-3 minutes for professionals.

The Bayley Infant Neurodevelopmental Screener (BINS) is a screening technique for determining infants at risk for developmental delay or neurological impairment aged between 3–24 months.

This technique is used for neuro-muscular functions (reflexes and muscle tone) and neurodevelopmental skills (motor and symmetry) and evolutionary achievements (language and imitation), consisting of 10-13 items. The scoring of this test is based on the mild, moderate and severe scores. Newsha "Newsha Developmental Scale", is a tool for assessing neurological development in areas of auditory, verbal language, cognitive, social connection. Information was entered into the tables for each instrument and the scores were calculated and compared with the normal range. Then the relevant information was entered into checklists, including variables information. Finally, a comparison of neurological growth between control and intervention groups was performed using the mentioned tools.

Statistical analysis

After collecting information by check list, they were encrypted and entered the computer. All data were analyzed using SPSS Statistics V22.0. The results for quantitative variables were expressed as mean and standard deviation (mean ± SD) and qualitative variables as percentages. P < .05 was considered statistically significant. Quantitative data and qualitative data were analyzed using t-student and chi-square, respectively.

4. RESULTS

In this study, 69.44% of the patients were male and 30.56% of them were female. As indicated in Figure 1, 22.22% of neonates had gestational age of 27 to 25 weeks, followed by 29-27 weeks (22.2%), 31-29 weeks (41.67), 33-31 weeks (8.33%), and 35 -33 weeks (5.56%) (Figure 1). Furthermore, 47.22% of patients were between the ages of 14-24 months, followed by 24-34 months (36.11%), and the age range of 34-44 months (16.67%).

The results presented herein indicated that 22.22% of babies had birth weight of 750-900 g, and 50% of them had a birth weight of 900-1050 g, and remaining neonates showed birth weight of 1050-1200 g (27.78%).

We identified that 30.56% of the infants were admitted for the first time at the beginning of birth for 30-45 days; 47.22% of them were admitted for 45-60 days and 22.22% of them for 60-75 days at the beginning of the birth. It is noteworthy that, all infants participated in the study were delivered by cesarean section. As shown in Figure 2, 25% of the patients with protein supplementation and11.11% of the patients without receiving protein were between 0-5 percentiles in terms of current weight. In addition, 8.33% of patients without protein supplementation and 5.56% of patients with protein intake were between 5^{th}-10^{th} percentiles. Also, 16.67% of patients with protein intake were categorized between 10^{th}-25^{th} percentiles. Furthermore, 8.33% of patients without protein supplementation and 11.11% of patients with protein use were divided between the 25th and 50th percentile. 8.33 percent of patients without protein intake were between 50th-75th percentile and 5.56 percent of patients with protein intake were categorized between the 75th and 90th percentile.

As shown in Figure 3 (based on the current stature), 16.67% of patients without protein supplementation and 5.56% of patients with protein intake were between 0-5th percentile, followed by 5th-10th percentile (8.33 without protein intake and 11.11% with protein intake), 10th-20th percentile (8.33% without protein intake and 11.11% with protein supplementation), 25th-50th percentile (5.56% with protein intake), 50th-75th percentile (16.67 % without protein supplementation and 16.67% with protein intake).Based on the result of current head circumference, 8.33% of patients without protein consumption and 11.11% of patients with protein use were categorized to be in the 5th-10th percentile, followed by a 5th-10th percentile (16.67% without protein intake and 5.56% with protein intake), the percentile of 10th-25th (8.33 without protein and 11.11% protein intake, 25th-50th percentile (8.33% without protein intake), percentile of 75th-50th (8.33% without protein supplementation and 11.11% with protein intake) and percentile 75th-90th (11.11% with protein intake (Figure 4).

BINS tool

Our findings revealed that there was no significant correlation between neurological growths and protein reception in the ELBW infants at the beginning of the birth by BINS tool in two groups (p = 0.266).

ASQ tool

We examined using this tool in five areas of communication, gross motor, fine motor, personal and social (individually) problem-solving in two groups.

Area of communication

Our data demonstrated that that there was significant correlation between neurological growths and protein reception in the ELBW infants at the beginning of the birth by ASQ tool in two groups (p = 0.014).

Gross motor areas

Using the ASQ tool, a significant relationship was found between neurological development and protein reception in the ELBW infants in the area of gross motor at the beginning of birth in both groups (p=0.001).

Fine motor areas

In the case of ASQ, no significant relationship was found between neurological development and protein reception in the ELBW infants in the area of fine motor in both groups at the beginning of the birth (p = 0.63).

Problem solving areas

According to ASQ, no significant relationship was observed between neurological development and protein reception in the ELBW infants in problem solving in of both groups (p = 0.07).

Personal-Social Sphere

Based on the results obtained with the ASQ tool, there is no significant relationship between neurological development and protein reception in the ELBW infants in area of the personal- social interaction in both groups at the beginning of the birth (p = 0.152).

NEWSHA tool

By this tool in seven areas of auditory, perceptual language domain, verbal language, speech, cognitive domain, social communication and motor (separately) was investigated in both groups.

Auditory areas

In this sphere, results showed that there was a significant relationship between neurological development and protein reception in the ELBW infants in terms of auditory in both groups, using NEWSHA tool information (p = 0.031).

Perceptual language domain areas

Using the information obtained from the NEWSHA Developmental Scale, there was no significant relationship between neurological development and protein reception in the ELBW infants in terms of the perceptual language domain in both groups (p = 0.168).

Verbal language areas

NEWSHA tool information showed that there is a significant relationship between neurological development and protein reception in the ELBW infants in verbal language in both groups (p = 0.024).

Speech areas

Based on the NEWSHA, there was no significant relationship between neurological developments and protein reception in the ELBW infants in area of speech among ELBW infants of both groups (0.379).

Cognitive domain areas

In the case of the NEWSHA tool, there is a significant relationship between neurological development and protein reception in the ELBW infants in the cognitive domain in ELBW infants of both groups (p= 0.007).

Social communication areas

In addition, based on the NEWSHA technique, a significant relationship between the neurological development and protein reception in the ELBW infants in the field of social communication among the ELBW infants of both groups (p= 0.034).

Motor areas

Using the NEWSHA tool, a significant relationship between neurological development and protein reception in the ELBW infants in the field of motor in both groups (p= 0.002).

On the other hand, our findings demonstrated that there was no significant difference in terms of the mean head circumference and protein reception in the ELBW infants in both groups (p=0.209).

Moreover, no significant difference between weight and protein reception in the ELBW infants in both groups (p= 0.217). Regarding the P value, there is no significant difference in stature among both groups (p=0.354).

5. DISCUSSION

Prevention of weight-loss via adequate nutritional supplementation is considered to be of great importance for managing preterm neonates during hospitalization. Improving growth characteristics can b. e highly affected by administering a nutrient-enriched diet, and neurodevelopmental outcomes can be also affected by this kind of supplementation (24, 25, 41). However, choice of appropriate nutrition has a special place, which variations in dietary nutrient can potentially be involved in growth deficits in preterm neonates (26, 27). The favorable growth of lean body tissue and the brain has been found to be related to protein intake of neonates (42).

In the present study, there was no significant relationship between neurological development rate evaluated by BINS tool in two groups (p=0.266). Cester et al. (2015) reported increasing intravenous and enteral protein intakes in the first month after birth lead to better early growth and decreased postnatal faltering growth, but was not capable of altering Bayley-III scores (i.e., cognitive, language or motor scores or sensory impairments), at 2 years' CA in studies infants (43). In accordance with Cester et al, our findings revealed that increasing protein intakes to recommended levels in the first month after birth was not linked to altering BINS scores.

Poindexter et al., 2006 suggested that early provision of parenteral amino acids can be involved in improved growth and neurodevelopment at 36 week PMA, where a low number of neonates were found to show suboptimal head growth at 18 months' CA (44). Another study indicated that early and high intravenous provision of amino acid (AA) in first week of birth have been previously demonstrated to be linked to impaired growth in ELBW children aged 2 years and BSID-II Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores was found to be markedly different in both groups, (ELBW children who received standard IV AA and early and high IV AA) (45).

On the other hand, early protein and energy intakes in first week of birth have been reported to be involved in developmental outcomes at 18 months and increased risk of growth retardation in Very-low-birth-weight (VLBW) neonates (46).

The tools used to study neurological growth, except for BINS and the same age, were different in our study and Cester et al. For this reason, our study is not fully comparable with this study. To the best of our knowledge, unfortunately, there was not a similar article that was completely comparable to our study.

The finding presented herein demonstrated a significant correlation between the neurological development assessed by the ASQ tool in the areas of communication and gross motor in the two groups. On the other hand, we found a significant correlation between neurological development evaluated with the NEWSHA tool in auditory, verbal language, cognitive, social connection and motor in the two groups.

Although an increasing body of evidence indicates the benefits of fortification with proteins including increased head growth, linear growth, and weight gain in preterm neonates, further larger trials are required to validate these findings. On the other hand, protein-alone fortification was not revealed to be involved in long-term growth and neurological development (37, 39, 40). The effect of high protein supplementation on neurological development is currently considered to be a controversial issue, where heterogeneous findings are published.

Our findings demonstrated no significant difference in the mean head circumference, weight and stature in both groups, where protein intake was not found to be associated with these variables. However, it has been indicated that early and higher protein and energy intake can be positively capable of affecting head growth and head circumference among preterm neonates, leading to better cognitive outcomes (47-49). The initial trial revealed that a high protein supplementation can lead to increased body and growth of head circumference, despite a remarkable late-onset sepsis in treated group (50). However, a randomized controlled trial was not effectively capable of showing the involvement of protein and fat in brain volumes and cognitive outcomes in preterm Infants, where afford mentioned study indicated that early energy deficit improvement in this infant may be capable of increasing brain growth (51).

In the current study, neonates at first week of their life received a protein supplement of 0.8-0.6 grams per day. Accumulating indicates supports that enteral intake of protein should be safe, where 3 to 4 g/kg/day protein intake can be capable of increasing growth in preterm neonates (40).

Several observational investigations demonstrated that enteral and parenteral protein supplementation can be positively linked to neurodevelopment during the first 7–10 days of birth in ELBW children (46, 52). In addition, an increasing body of evidence suggests supplementation of the preterm formulas or breast milk in conjunction with protein doses of 3.8 g/kg/day and 4.1 g/kg/day would increase cognitive development when comparing with lower doses of protein by applying neonatal behavioral assessment scale (NBAS) and Griffith mental development scales (GMDS) scales (22, 53). Contradictory results are published previously that indicated higher doses of protein (6 g/kg/day or more) in an enteral supplementation have been associated with detrimental outcomes (e.g., poor cognitive outcomes etc) (54). On the other hand, the evaluation time should be taken in to consideration in published literatures, where its effect on growth and neurodevelopment (e.g., neurocognitive outcomes) revealed a controversial issue (44, 55).

6. CONCLUSION

The results presented herein, indicated that protein intake in premature infants at first week of life was not capable of affecting the growth rate of head circumference, linear growth, and weight in the long term. Furthermore, the protein intake of preterm infants was found to be associated with improved neurological development assessed by the ASQ tool in terms of communication and gross motor.

Additionally, protein intakes to recommended levels in the first week of life was found to be linked to improved auditory, verbal language, cognitive, social connection and motor by using NEWSHA tool.

Protein intake in the first week of life did not effect on neurodevelopmental outcomes in the areas of fine motor, problem-solving, and personal-social (based on the ASQ), as well as the domains of speech and perceptual language (NEWSHA) and the neurological development examined by the BINS tool. Further larger trials are required to achieve more favorable and definitive results and to defined better assessment time point and protein intake doses for favorable and/or deleterious outcomes as well as long-term safety in VLBW preterm babies.

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- **Author's contribution**: MK, FMS, and AB gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. MK, FMS, and AB had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they are agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflicts of interest**: There are no conflicts of interest.
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