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Effect of Fortified Complementary Food on Iron Stores and Growth in Infants with Cleft Lip Palate–A Study Protocol for Randomized Control Trial

Study Protocol

Kashamma V Uppin[1]*, Rajesh S Powar[2] and Roopa M Bellad[3]

[1]*Department of Public Health, Lecturer- Nutrition, JNMC, KAHER, Belagavi, Karnataka, India*

[2]*Department of Plastic and Reconstructive Surgery, HOD, Professor, JNMC, KAHER, Belagavi, Karnataka,India*

[3]*Department of Paediatrics, Professor, JNMC, KAHER, Belagavi, Karnataka, India*

***Corresponding author:** Kashamma V Uppin, Department of Public Health, JNMC, KAHER, Belagavi, Karnataka, India, E-mail Id: uppinkashamma@gmail.com

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Abstract

Aim: To assess the effect of fortified complementary food in Infants with Cleft Lip Palate on Iron Stores, Growth and Neurodevelopment at 12 months.

Design: We devised a study protocol for a randomised controlled trial, which will be conducted between Nov 2022 and Nov 2024 in tertiary care hospital with studypopulation of 130 infants with cleft aged 6 months. Eligible infants with cleft attending outpatient department will be recruited into the trial after obtaining consent.

Participants: One hundred and thirty-five eligible participants will be randomly assigned to a control group, receiving unfortified complementary food and to an experimental group receiving fortified complementary food for the duration of 6 months. Primary outcome of the study is to see improvement in body iron store as measured by Hemoglobin, S Ferritin, S Iron, TIBC and S Zinc and Secondary Outcome is improvement in growth in terms of weight, length and head circumference and Neurodevelopment Assessment using the Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III)

Expected Outcome: To achieve optimal growth in infants with cleft lip and palate and be ready for timely surgery, it is critical to implement appropriate nutrition interventions and nutrition education to the family. It's a study protocol and expecting a change in body iron stores by 20% and improvement in growth and neurodevelopment of the infant with cleft.

Ethics and Dissemination: This study is approved by Institute's Ethics Committees. The results will be disseminated through peer-reviewed publications and presentations targeting the global and local research communities. Trial registration number: CTRI/2022/11/047579.

Introduction

Nutrition is one of the easily modifiable environmental factors that can affect growth, development, infant metabolism, and the immune system. Good nutrition during first thousand days of life is critical and crucial for healthy growth and neurological development across the lifespan. Nutrition during this period is of importance because it positively affects the child physical and cognitive development.[1] Introduction of complementary feeding which should begun from 6 months onwards is associated with major changes in both macronutrient and micronutrient intake.[4] This period is characterized by rapid development and growth, exposing infants to an increased risk of deficiencies, especially Iron Deficiencies and Iron Deficiencies Anaemia, which are most common at this age affecting an estimated 40% of children under five years of age in both low- and high-income countries.[1] Consequently, complementary foods and correct feeding practices can prevent malnutrition.

Infants born with cleft lip and or palate have problems with feeding in varying degrees. The extent of feeding problem and malnutrition varies with the severity of defect.[2] Irrespective of the setting, infants born with an orofacial cleft have a heightened risk of failure to thrive because their ability to suck and swallow is compromised.[6] Malnutrition in infants with cleft can be attributed

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to feeding challenges like poor oral suction, lengthy feeding times, nasal regurgitation, excessive air intake, and inadequate volume of oral intake.[2] Infants with CLP presents with unique nutritional requirements and vulnerabilities.[3] Infants born with clefts require prompt nutrition support to be ready for timely surgery. Maintaining sufficient dietary intake is of paramount importance to build their immunity and to allow adequate weight gain so that they can tolerate stress of surgical interventions and hasten the healing process.[5]

Global estimate of malnutrition in children with cleft, born in limited-resource settings is about 28% at the time of primary surgery which is well above the global underweight prevalence in under-5 children without cleft estimated at about 13·5%.[6] From a study conducted in India, 69.6% children with cleft below the age of 5 years were malnourished. As per the WHO classification, 12.5% of children were severely malnourished and 34.8% were mildly malnourished.[7] Prevalence of all forms of malnutrition particularly wasting among clefts is much higher than the national average.[8] Infants are more susceptible to micronutrient deficiencies and the most common one is anemia because of feeding difficulties where the infant with cleft consumes less nutrients and repeated upper airways or middle ear infections.[8] Iron deficiency with or without anemia in the first 6 months of life can adversely affect child's physical and cognitive development. The child with anemia is more vulnerable to infection and has lower immunity. In infant with cleft, it also adversely affects their wound healing in post cleft repair.[8]Few studies report the prevalence of anemia among cleft (74.6%) higher than the national average.[8]In another study, anaemia (microcytic hypochromic type) was reported as 81.63% and eosinophilia was seen in 20.60% cases which interferes with and delays the surgical management of these patients. [9]

Body iron stores as measured by serum iron, serum ferritin was much lower among children with cleft lip and/or palate when compared to that of age-matched controls. The iron deficiency state has no relation to the type of cleft present.[8] The other micronutrient deficiencies commonly seen among children with both cleft lip and palate are folate and vitamin B12 deficiency, compared to children having only one of the two deformities.[8] Malnutrition among patients with CLP is further exacerbated by surgical intervention, wound healing and impaired postoperative feeding until the surgical site heals. Surgery and wound healing results in a hypermetabolic state during the postoperative period as the body responds to tissue damage in turn increasing the demand for good nutrition.[8]

Most common type of malnutrition is protein deficiency and micronutrient deficiencies.[11] Protein deficiency in infants with cleft is characterized by stunted growth, lack of muscle mass, oedema and delayed healing. The oedema and poor muscle mass might lead to a compromised outcome of lip and palate surgeries attributed to tension on the surgical closure line.[11] Malnutrition among infants will have negative effect on surgical healing.[3] Poor perioperative nutrition has been associated with higher complication rates in other disciplines. Good nutrition plays a major role in surgical wound healing and improves the surgical outcome.

Infant and young child feeding (IYCF) practices like early initiation of breastfeeding, exclusive breast milk feeding, starting of complementary feeding at 6 months, dietary diversity which are suboptimal among under 5 infants both in with and without cleft are the major reasons for malnutrition [7,10] Therefore, overcoming nutritional inadequacies and providing nutrition information to parents is critical in combating feeding issues and ensuring that infants receive proper nourishment. Introduction of nutritious complementary food during the perioperative stage which will help in wound healing, quicker recovery from surgery and growth is of paramount importance. Dietary diversification, fortification of complementary foods and nutrition education are important measures to improve the overall nutritional quality of the child's diet which in turn reflects in timely ready for surgery.[12]

Materials and Methods

Development of Product

Infant of 6 -12months consumes small quantity of food hence it is imperative to provide optimum nutrition at every meal. Home-based meals, predominantly vegetarian may lack in many micronutrients which creates a nutrition gaps and results in hidden hunger.[19] In this context, iron fortification of complementary food made from locally available grains to meet iron gap provide effective strategy to combat malnutrition. Role of iron in neurodevelopment, cognition and immunity during infancy cannot be undermined. [19] According to National Health Family Survey 5 prevalence of anemia among children age 6- 59 months is 67% and among infants with cleft is 74%.[18] Zinc deficiency is associated with poor growth, loss of appetite, skin lesions, impaired taste acuity, delayed wound healing, hypogonadism, delayed sexual maturation, and impaired immune response. Zinc is widely present in all food groups but the bioavailability is low because of high amounts of inhibitors such as fibre and phytate.[20] Hence it is important to fortify complementary food with micronutrient to meet the gap. For this study a low-cost complementary food will be prepared by mixing malted pearl millet, roasted amaranth, roasted green gram. The domestic processing of grains like soaking, germination and roasting will result in lower levels of phytic acid, polyphenols and saponins and higher bioavailability of proteins, iron and zinc than those of the raw grains used for preparing mixtures. Food legumes are good source of protein and continue to contribute significantly towards the protein content of diets of people. Food fortification is one of the most cost-effective ways of addressing development challenges in infants according to 2008 Copenhagen Consensus. [22] Report from meta-analysis, which included 18 randomized controlled trials and 5468 children, compared the impact of micronutrient-fortified milk and cereal- based products versus similar non-fortified items on children between 6 months and 5 years of age. The use of fortified milk and cereal-based products was more effective in reducing anemia in young children in developing countries, compared to the use of non-fortified products.[22] On this rationale, study complementary food was prepared by the above method and fortified with iron, zinc and vitamin C and then evaluated for its nutritional characteristics. Points to be considered when a food product is fortified with a trace element is safety, beneficial effects of the trace element, influence on the organoleptic properties of the food, and cost of the fortification. Vitamin C was added to increase the iron absorption. This product

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was developed and fortified as homemade and commercially available food lacks micronutrients. Millet was used to bring in the dietary diversity. The formulation was prepared in accordance to national standards. Malt is fortified with ferrous fumarate, zinc sulphate and vitamin c to achieve 75% of recommended allowance in per serving to achieve 20% change in body iron stores. Study using ferrous fumarate (FeF) as an iron compound, had stronger effect on iron status with higher Hb and serum ferritin (SF) concentration and reduced anemia and ID in infants receiving additional 5.5 mg or 12.5 mg iron per day from a micronutrient-fortified maize porridge compared with their control peers. [20,23] Fortified complementary food and the unfortified complementary food is evaluated by atomic absorption spectrophotometer method. A 5 g sample was dried and ashed in a muffle furnace at 550^{0}C temperature and the residue dissolved in 6 N, 1:1 hydrochloric acid. Iron and Zinc concentration of the sample was estimated using the Atomic Absorption Spectrophotometry. Other nutrient contents of malt were estimated using national food tables. Each serving of fortified malt (25gms) contains 3.92mg of iron and 3.87mg of zinc when compare to unfortified malt (Iron – 1.29mgs and zinc 0.69mg). [23]

Study design

This study is a randomized clinical trial. The trial will be performed in tertiary care hospital in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement. The protocol is registered in the Clinical Trial RegistryCTRI/2022/11/047579. Approval for the study was granted by Institute's Ethics

Committees on Human Subject

Study population: Infant with Non syndromic cleft lip and or palate of 6 months of age.

Inclusion criteria

1) Cleft lip and or palate infants of age 6 months and above attending the Out Patient Department

2) Parents who give consent for the study.

Exclusion criteria

- Infants with syndromes or with secondary deformities were excluded.
- Any congenital heart disease

The study population includes a total of 130 infants aged 6 months non syndromic cleft, who will be recruited into experimental group (n 65) or control group (n 65). A sample size of 65 infants per study group was required to detect an expected difference of 20% in increase Hb concentration between the baseline and endpoint results of intervention group, with statistical power of 95%.

Baseline Assessment

Baseline data will be collected at the time of recruiting of the eligible study participants. Data on socio-economic status, anthropometric measurements, bio-chemical data, clinical history and signs, and dietary history. Blood sample will be collected for Body Iron store and S Zinc assay.

Randomization and Allocation

Eligible subjects will be randomly allocated into one of the two groups according to a computer-generated randomisation list. Study participants at the time of recruiting will be allotted one of the following two groups;

Group 1**: C**omplementary food or fortified complementary food for a duration of 6 months.

Intervention

Study participants will consume 25g of complementary food per day for 6 months of intervention in addition to the habitual complementary feeding regimen. The fortified complementary food provided 75% of the daily recommended intake for iron and zinc so that other complementary foods or breast milk could still contribute to the DRI. Depending on the infant's age and feeding behavior, caregivers will be instructed to cook and feed 25 g of infant cereal. Caregivers will be instructed to reconstitute 25g complementary food with 150 ml of water and cook for 5 minutes to obtain a puree consistency allowing to feed the infant cereal with a spoon. Consumption of study malt amount (25gm) is constant and supports growth metrics of infant as the requirement for 6-12months is same. Along with this intervention, caregivers are encouraged to follow Infant and Young Child Feeding practices for optimal growth.

Post-baseline assessments will be conducted at midpoint (9 months of age) and at study end (12 months of age).

Primary outcome of the study is to see improvement in body iron store as measured by Hemoglobin, S Ferritin, S Iron, TIBC and S Zinc because the study malt is fortified with iron and zinc. Anthropometric measurements will be measured at 9th and 12thmonth. Weight-for-age, length-for-age, weight-for-length, and head circumference-for-age Z- scores will be calculated using WHO reference data. Concomitant medications, including the use of iron supplements based on a low Hb concentration during a study visit, will be monitored throughout the study. Morbidity and safety will be assessed from 1) a sickness questionnaire at baseline, midpoint, and study end visit, 2) recording of adverse events (AEs) will be collected during each visit for both groups. Nutrient intake will be evaluated using a 24- hour dietary recall administered by a trained dietitian to the infant's parent or caregiver at baseline and all the study visits for the both the groups. Breastmilk intake during the 24-hour dietary recall was assessed as frequency of breastmilk feeds. The daily intake of energy, macronutrients (fat, carbohydrates, and protein) and selected micronutrients (iron, and zinc) coming from complementary food and regular diet will be calculated using Food Composition Tables. Adherence to the dietary intervention will be measured by subjective methods like 24 h dietary recall method and food frequency questionnaire and objectively byimprovement in weight gain, body iron store and ultimately eligibility for surgery.At 12th month, Neurodevelopment Assessment using the Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III) will be assessed.

Data Management and Analysis

A total of 130 infants with cleft will be screened for enrollment in

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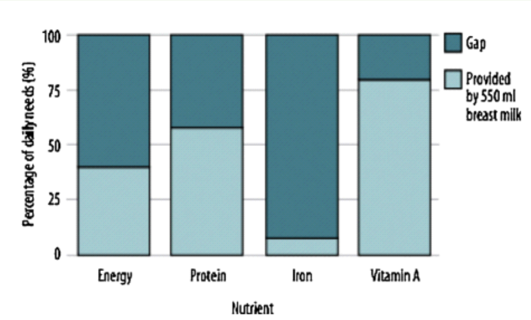

Figure 1: Gaps to be filled by complementary foods for a breastfed child aged 12–23 months.

the Control group and Study group. During the intervention, maternal and infant characteristics like ratio of boys to girls, mean birth weight, gestational age, mode of delivery and breast feeding will be compared between the two groups for any statistical differences. Students T test will be applied for testing means. The socioeconomic status will be studied. Iron status assessed by Hemoglobin, Serum Ferritin and Serum Transferrin concentrations and Bayley-III scores between the study group will be compared using analysis of covariance (ANOVA). Chi square test will be applied for categorical data. At 12 months of age growth outcomes in the two groups will be compared by similar anthropometric Z-scores. Frequency of breastfeeding, energy and nutrient intakes between the two study groups were compared by independent t-test. With nutrition education and complementary food provision, growth should be improved. Dietary intake will be assessed by 24 hours recall as given by the care taker. With nutrition support and education expect an improvement in dietary diversity and in turn overall growth and development. Neurodevelopment at 12 months of age will be assessed using the Bayley-III score for both the groups. Many areas of child development are negatively affected in infants with Cleft lip and/or palate. With improvement in body iron stores and growth, we expect to see improvement in neurodevelopment. Adverse events and concomitant medication will be recorded during the visits.

Discussion

Malnutrition and anemia prevent many children with OFC from receiving timely surgical care. Exclusive breastfeeding up to 6 months of life is associated with better iron status in infants as it provides highly bioavailable iron and reduces diarrheal diseases (and other infections). Most infants with cleft do not receive breastmilk because of feeding challenges. Use of formula feeds, unhygienic conditions lead to repeated infection and hence malnutrition and anemia. Nutritional inadequacies can be tackled through diet diversity, food fortification and nutrition education. We assume, in our randomized control study among infants with cleft lip palate aged 6 months who will receive fortified complementary food for 6 months will have better body iron stores at 12 months of age and lower rates of Iron Deficiencies and Iron Deficiency Anemia than infants who will receive the only complementary food. Homemade complementary food often is low in iron concentration and bioavailability and do not cover the high iron needs during rapid growth in infancy. Hence, the need for fortification of complementary food to support the rapid growth and development in infants

Conclusion

First 1000 days is the "critical window" for the promotion of optimal growth, health, and cognitive development. Malnutrition in infancy especially in infants with cleft can be attributed to feeding challenges and inadequate infant feeding practices. To achieve optimal growth in infants with cleft lip and palate, it is critical to implement appropriate nutrition interventions and nutrition education to the family. The goal is to provide the newborn with enough nourishment before and after surgical intervention so that the infant recuperates well.

Ethics and Dissemination

This study is approved by Institute's Ethics Committees on Human Subject. The results will be disseminated through peer-reviewed publications and presentations targeting the global and local research, clinical, program implementation and policy communities.

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