Original Article

An open-label, pilot study to evaluate the benefits of using lyophilized human milk-derived nutritional product (NeoLact 70 – 1.55 g) as an immune-nutritional supplement in premature infants discharged from NICU

Gowtham R[1], Anisha Afza[1], Shankar[1], Lingaraju Subbanna[2]

From [1]Fellow Trainee, [2]Consultant Neonatologist, Department of Neonatology, People Tree Meenakshi Hospital, Bengaluru, Karnataka, India

ABSTRACT

Background: Premature and low birth weight (LBW) infants are at increased risk of having inadequate growth in post-discharge periods. In this study, lyophilized human milk was used as an immune-nutrition supplement along with breastfeeding for a period of 1 month in preterm infants discharged from neonatal intensive care unit (NICU). **Objectives:** Primary objective was to assess the percentage change in serum immunoglobulins for the duration of supplementation, and secondary objectives were to correlate changes in immunoglobulins to number of episodes of infections including respiratory infections and diarrhea, requirement of antibiotics, weight gain, and episodes of feed intolerance during the study period. **Methods:** A total of 10 preterm and LBW infants were included in the study at the time of discharge from NICU after satisfying the inclusion and exclusion criteria. The serum immunoglobulins were estimated at baseline and at end of the study, other parameters such as episodes of infections, feed intolerance, and weight gain were recorded on the weekly follow-up visits. All the infants received supplementation with NeoLact 70 – 1.55 g on a TID frequency along with the regular breastfeeding for a period of 1-month post-discharge from NICU and were followed up on a weekly basis. **Results:** Ten infants completed the study, mean birth weight and gestational age were 1779.4±576 gm and 33.5±4.9 weeks, respectively. There was increase in immunoglobulins IgA, IgE, IgG, and IgM by 38.29%, 85.36%, 17.45%, and 48.25%, respectively, from baseline to end of study. None of the infants experienced feeding intolerance, diarrhea, abdominal distension, fever, respiratory infections, or rehospitalizations, none of the infants required antibiotics or probiotics during the study period. The average weight gain in the 1st, 2nd, 3rd, and 4th week of supplementation was 28.42 g/day, 31.57 g/day, 35.17 g/day, and 39.24 g/day, respectively, with a mean weight gain of 30.4 g/day achieved for the entire duration of the study. **Conclusion:** The immune-nutritional supplementation with lyophilized human milk (NeoLact 70 – 1.55 g) helps to ensure exclusive human milk diet post-discharge and reduce the risk of infections, diarrhea, and rehospitalization through the enhancement of immunoglobulins and ensuring optimal weight gain. However, these results should be confirmed through multicentric studies with larger sample size. Supplementation with NeoLact 70 – 1.55 g can clinically benefit premature and LBW infants post-discharge.

Key words: Prematurity, Low birth weight, Human milk, Post-discharge nutrition

Prematurely born infants require greater nutritional support than term infants for adequate growth and development even post-discharge [1]. Premature and low birth weight (LBW) infants admitted in neonatal intensive care unit (NICU) with a history of sepsis, respiratory infections, and poor gut health would require optimal nutrition along with protection against common microbial infections post-discharge. Infections are common in the first 2 years of life, children under 2 years' experience an average of 3–5 episodes of diarrhea per year in developing countries. Risk of having diarrhea increases through mixed feeding with bovine milk-based nutritional supplements and more so in the post-discharge period. During an infection episode, the immune system requires a broad range of nutrients to mount a defense against the invading organisms. It has been hypothesized that nutritional interventions targeting growth may not be effective if infections are prevalent. On the other hand, improved nutrition may strengthen the infant's ability to fight infections and reduce the negative effects of infection on growth. Human milk is a rich source of bioactive proteins which provides both nutritional and protective supports for the growth of a newborn. It is a well-recognized fact that benefits of human milk extend beyond nutrition, by reducing the risk

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Correspondence to: Dr. Gowtham R, Department of Neonatology, People Tree Meenakshi Hospital, Bengaluru, Karnataka, India. E-mail: neopublication@gmail.com

for both early and late complications for the newborn. Hence, ensuring exclusive human milk diet (EHMD) post-discharge is equally important for premature newborns [2,3]. Therefore, human milk is essential to meet the demands of macronutrients for infants who are at risk of infections, poor growth, and poor gut health.

NeoLact 70 – 1.55 g (NeoLacta Lifesciences Pvt. Ltd.) is a lyophilized human milk, which retains both nutritional and immunological properties of human milk including immunoglobulins, human milk oligosaccharides, and nucleotides. Hence, it can be beneficial as a post-discharge nutritional supplement for preterm infants, which may help in reducing the risk of post-discharge infections. NeoLact 70 can be used in addition to breastfeeding to strengthen the immune-nutritional status in the infants, it can also be used as supplementary nutrition when mother's own milk is insufficient or not available. At present, there is a dearth of scientific data available in India on the benefits of using a human milk-derived nutritional product as a post-discharge nutritional option for infants. NeoLact 70 is a 100% human milk-derived nutritional product, made available in India for the 1st time which can provide multifactorial benefits. Hence, this study will be vital to assess the beneficial effects of NeoLact 70 as a post-discharge immune-nutritional supplement for preterm infants.

MATERIALS AND METHODS

This was an open label, exploratory study conducted on 10 preterm infants who were discharged from the NICU of People Tree Meenakshi Hospital in Bengaluru. The study was conducted between September 2020 and November 2020. Institutional Ethics Committee approval was obtained before the initiation of the study. An informed consent was obtained from the parents of all infants, after describing the study in detail.

Preterm and LBW infants, discharged from NICU, were included in this study who had one or more of the following criteria: (a) At least one episode of sepsis/infection during the NICU stay, (b) feed intolerance during the NICU stay, (c) poor growth during NICU stay, (d) recurrent infections/diarrhea, and (e) infants receiving vaccination and on formula/mixed feeds. Infants with major congenital malformations or intestinal anomalies and infants with intraventricular hemorrhage, cardiac-, liver-, and kidney-related complications, were excluded from the study.

Primary outcome was percentage change in serum immunoglobulins from baseline to end of the study and secondary outcomes were following parameters which were observed during each outpatient department (OPD) visit: (a) Number of episodes of fever, (b) number of episodes of tachypnea or noisy breathing, (c) number of episodes of reduced feeding, (d) weight gain (e) number of days requiring antibiotics, and (f) feed intolerance defined as number of episodes of vomiting, diarrhea, and abdominal distension.

Feeding Protocol

Study was initiated after receiving the approval from the Institutional Ethics Committee and informed consent was obtained from the parents before the commencement of the study. Ten infants who fulfilled the inclusion criteria were enrolled into the study. NeoLact 70 – 1.55 g was initiated at the time of discharge and was used with breastfeeding as an immune-nutritional supplement, at a frequency of 3 sachets per day. Feed preparation instructions were provided to the mothers by the nursing staff at the time of discharge. NeoLact 70 was to be mixed in 10 ml of sterile water and fed to the infant. Data were collected in the case report forms as per the primary and secondary end points. Study was continued for 4 weeks from the day of discharge, subsequent to which the feeding regimen for all the infants in the study was determined by the treating neonatologist. Immunoglobulin profile was analyzed through serum samples taken at baseline (before starting NeoLact 70) and end of the study. All other treatment modalities were as per the hospital protocol and guidelines.

RESULTS

Ten infants were enrolled over the 3-month study period between September 2020 and November 2020. The baseline characteristics of the study subjects and the medical history of study subjects before the study are described in Table 1.

Results obtained on the primary outcome, percentage change in the immunoglobulins from baseline to end of the study is described in Fig. 1.

Two infants experienced one episode of vomiting each which was unrelated to the supplementation with NeoLact 70, as per the temporal relation to the feed intolerance episodes. None of the infants in the study experienced diarrhea, abdominal distension, fever, or respiratory infections. Two infants had one episode of reduced feeding each, none of the infant required antibiotics or probiotics for the study duration. None of the infants had readmissions or OPD visits for any health-related issues during the 4 weeks of supplementation with NeoLact 70. Mean weight gain was 30.4 g/day from baseline to end of the study. Fig. 2 shows the week wise weight gain pattern from baseline to end of study with an average weight gain in the 1st, 2nd, 3rd, and 4th week.

Table 1: Baseline characteristics

Parameter	(n=10)
Birth weight (g), mean±SD	1779.4±576
GA (weeks), mean±SD	33.5±4.9
Male, %	60
Continuous positive airway pressure during NICU stay, %	70
H/O sepsis during NICU stay, %	40
H/O jaundice, %	90
Duration of parenteral nutrition (days), mean±SD	7.33±4.2
H/O infants with poor weight gain during NICU stay, %	60

SD: Standard deviation, NICU: Neonatal intensive care unit, GA: Gestational age

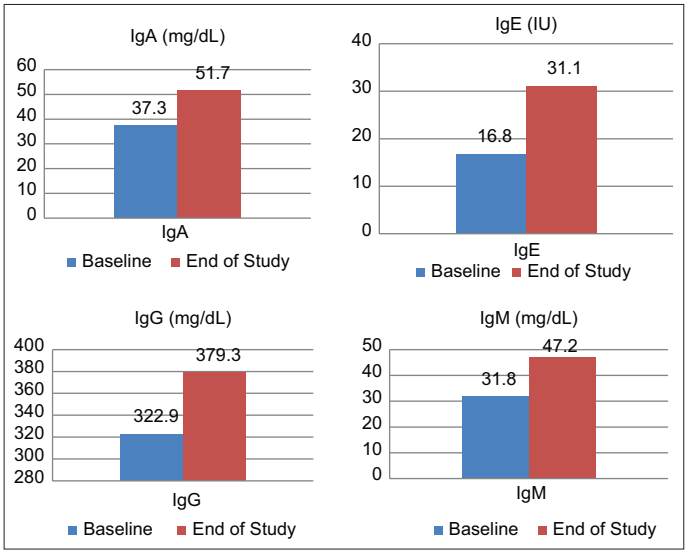

Figure 1: Observed change in immunoglobulins IgA, IgE, IgG, and IgM profiles

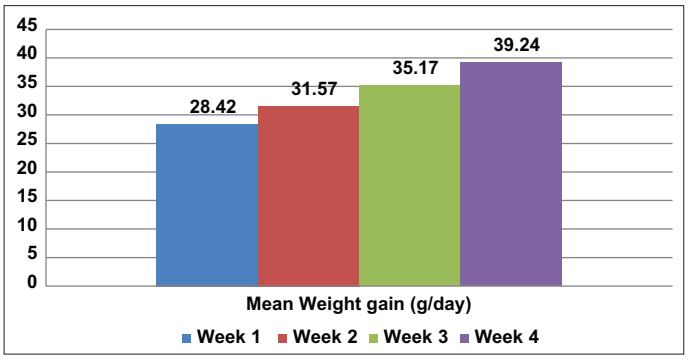

Figure 2: Observed change in weight during the study period

DISCUSSION

Premature babies are inherently predisposed to a higher risk of morbidity and mortality. LBW and prematurity are among the leading causes of infant mortality after congenital anomalies. There is a higher risk of sepsis in preterm infants due to the immature immune system; occurrence of infective episodes in NICU would lead to extended hospitalization with the additional burden of using antibiotics. Almost 50% of preterm and LBW neonates admitted to NICU carry the risk of developing sepsis [4]. Risk of developing infections is more during the early post-discharge period, which is due to the suboptimal defense against infective microorganisms by neutrophils, macrophages, T-cells, and immunoglobulins, importantly IgG and IgA [5].

Usually, newborns acquire humoral immunity from IgG which is transferred to the fetus starting between the 8th and 10th weeks of gestation and surges during the last trimester. A preterm infant misses out this crucial period which can result in immunoglobulin inadequacy, thus increasing the risk of sepsis during early and late neonatal periods [6]. Preterm infants also have a risk of suboptimal growth post-discharge, hence, there is a need for an effective post-discharge nutritional support in addition to breastfeeding [7,8].

Studies have provided evidence that infective episodes, especially infections causing diarrhea, have a negative impact on the growth of infants, which can be reduced by providing optimal nutrition. Interventions that combine improved nutrition with prevention and control of infections are likely to be most effective for enhancing child growth and development and only human milk can provide both nutrition and immunity for the newborn infants [3]. This study was conducted to assess the effect of supporting breastfeeding with a human milk-derived nutritional supplement on immunoglobulins, incidence of infections, and weight gain in immediate post-discharge periods for preterm and LBW infants.

A study by Naural *et al*. had observed that average count of serum immunoglobulins IgG, IgM, and IgA in term infants between 0 and 6 months would be 941 mg/dl, 46.7 mg/dl, and 27.8 mg/dl, respectively, where the IgG was showing a consistent reduction from cord blood up to 12 months of age [9]. Another study done by Ballow *et al*. who showed that in preterm infants between 29 and 32 weeks gestational age (GA), the immunoglobulins IgG, IgM, and IgA from serum sample was 368 mg/dl, 9.1 mg/dl, and 0.6 mg/dl at 7 days of life and 123 mg/dl, 15.2 mg/dl, and 3.0 mg/dl at 2 months of life, respectively [10].

Although there is a large variation between studies with different characteristics such as GA, birth weight, and method of immunoglobulin assay, there is no consensus on the normal range of serum immunoglobulins for premature and LBW infants. In our study, we noticed that IgA increased by 38.29% (37.3–51.7 mg/dl), IgM increased by 48.25% (31.8–47.2 mg/dl), IgG increased by 17.45% (322.9–379.3 mg/dl), and IgE increased by 85.36% (16.8–31.1 IU). We also observed that increase in immunoglobulins had a clinical impact, where none of the infants had rehospitalization, sepsis, respiratory infections, or diarrhea. None of the infants needed any antibiotics or pre/probiotics during the study period. This may indicate the clinical benefit of human milk-derived supplementation used in this study, which in a lyophilized form retains immunoglobulins from donor human milk. This can provide the preterm infants with additional immunoglobulins, including secretory IgA enrichment which plays an important role in reducing the risk of gastrointestinal infections [11].

Fadnis *et al*. observed the weight gain pattern for 1 month of preterm infants who were discharged with an average weight of 1777 g, where infants were discharged on breast milk fortification with a bovine milk-based fortifier. Average weight gain was 20.7 g/day, 27.28 g/day, and 11.8 g/day by the end of week 1, week 2, and week 4, respectively, with an overall average weight gain of 17.03 g/day achieved from discharge to 1-month post-discharge period [12]. In our study, supplementation of breastfeeding with lyophilized human milk on TID basis showed a weekly average weight gain of 28.42 g/day, 31.57 g/day, and 39.24 g/day by the end of week 1, week 2, and week 4, respectively, with an overall average weight gain of 30.04 g/day achieved from discharge to 1-month post-discharge period. These results provide preliminary evidence on the benefits of continuing EHMD even post-discharge for premature and LBW infants. In our study, we observed that ensuring EHMD post-discharge with supplementation of lyophilized human milk improved serum

immunoglobulin levels which clinically correlated with having no incidences of infections, diarrhea, or rehospitalization. In addition, weight gain was optimal during the entire period of supplementation.

CONCLUSION

In this study, we observed that human milk-derived nutritional supplement (NeoLact 70 – 1.55 g) can help in ensuring EHMD post-discharge. This helps reduce the risk of infections, diarrhea, and rehospitalization through enhancement of immunoglobulins and ensures optimal weight gain. Supplementation with NeoLact 70 – 1.55 g can clinically benefit the premature and LBW infants discharged from the NICU. These results are from a pilot study with limited sample size and hence would need a multicentric standard control study with larger sample size to confirm the benefits.

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