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Original Research Article

Does full enteral feed from day one of life influence weight gain in hemodynamically stable VLBW babies weighing between 1000-1500 grams as against standard feeding? an open label randomized controlled trial

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ABSTRACT

Background: Preterm neonates post-natal growth should be similar to the intrauterine growth of the fetus of the same gestational age. This study aims to evaluate the effects of full enteral feed (60 ml/kg/day of human milk on day one, 20ml/kg/day during feeding advancement) started from day one of life (intervention) in enhancing the regain of birth weight compared to that of standard feed (both human milk feeds and intravenous fluid) in a group.
Methods: Babies were started on enteral feeds with human milk at the rate of 60ml/kg/day from day one and progressed by increments of 20 ml/kg/day up to maximum enteral feed of 180 ml/kg/day. The primary outcomes like Number of days taken to regain the birth weight, Duration of hospital stay, Incidence of Necrotising Enterocolitis (NEC), Incidence of sepsis, need for intravenous fluid therapy was assessed and statically analysed.
Results: Full enteral feeding group infants had lesser days of intravenous fluids. Full enteral feeding group regained birth weight at a mean age of 17.37±4.9 days and in the standard feeding group, birth weight was regained at a mean age of 19.8±4.3. Full enteral feeding group regained birth weight at a mean age of 13.12±2.17 days and in standard feeding group at a mean age of 15.38±3.57and this was statistically significant (p - 0.009). Full enteral feeding group babies had lesser number of days of intravenous fluids compared to babies in standard feeding group. It was statistically significant (p - 0.003).
Conclusions: Full enteral feeding practices from day one of life with human milk is feasible, cost effective and safe in hemodynamically stable VLBW infants and results in earlier regain of birth weight.

Keywords: Full feed, Hospital stay, Necrotizing enterocolitis, Preterm, Randomized control trail

INTRODUCTION

Preterm neonates post-natal growth should be similar to the intrauterine growth of the fetus of the same gestational age.[1] But, most of the preterm very-low-birth weight infants ended up in a growth-restricted state called extra uterine growth failure.[2] Introduction of enteral feeding is delayed in these babies due to the fear of feed related issues. They enter into a catabolic state, which results in poor neurodevelopmental outcome. Early nutrition and neurodevelopment is closely linked. There is a critical window of opportunity from birth to regain of birth weight where optimal nutrition has its greatest benefit.[3] In utero fetus constantly swallows amniotic fluid which plays an important role in growth and development of GI tract. Postnatally, enteral feedings

also stimulate the motility of the GI tract and various hormonal secretions.[4-6] Initiation of early feeding outweigh the issues that can crop in VLBW babies. Neonates are lacking in secretory IgA at birth. Maternal colostrum contains high concentrations of IgA helps in the development of innate immunity in the Payer's patches of the small intestine. Human milk contains immunoglobulin of which IgA is 67-100% and remains consistently high whereas other immunoglobulin decreases over time with lactation.[7] Delayed initiation of feeds leads to villous atrophy, decreased hormone and enzyme production, delayed functional maturation of the GI tract and results in abnormal microbial colonization.[8] This may ultimately lead the gut at risk for NEC and prolonged use of parenteral nutrition.[9] All these factors result in increased risks of late onset sepsis, cholestatic jaundice and vitamin and mineral deficiencies and longer duration of hospital stay.

Breast milk of biological mother is the ideal for babies. When it is not available the next best option is the donor milk because of the lower incidence of necrotising enterocolitis, septicaemia and better feeding progression when compared to the use of formula feed. At present there is wide variation in feeding practices in VLBW infants. Early introduction of enteral feeds is advantageous in resource limited settings where the availability and usage of TPN is limited and severe infection (septicaemia, pneumonia) is an important cause of mortality and morbidity.

Delayed versus early introduction of progressive enteral feeds

Cochrane review including seven RCTs with 964 babies concluded that there was no difference in the incidence of NEC between early (up to 4 days after birth) or late (later than 5-7 days after birth) introduction of progressive enteral feeds for preterm, VLBW babies.[10] Sub group analysis of these trials also concluded that there was no statistically significant effect on the risk of NEC even in growth-restricted infants with abnormal umbilical artery Doppler flow.[11]

Slow versus faster advancement of enteral feed volumes

The Cochrane review 2013 of five randomised controlled trials with 588 infants comparing slow advancement (defined as 15-20ml/kg/day) and faster advancement (30-35 ml/kg/day) concluded that no statistically significant increase in incidence of NEC among both the groups.[12] The babies in slow advancement group took longer time to regain birth weight (median difference 2-6 days) and establish full enteral feeds. Feeding human milk improve feed tolerance in preterm VLBW neonates. Schanler et al, in his study found that babies receiving at least 50ml/Kg/day of human milk had decreased number of feed intolerance and reached full enteral feeds rapidly.[13] Hence we want to assess the initiation of full enteral feeds from day one of life using exclusively human milk. This trial also gives confidence for mothers for achieving successful lactation as well as health personals.

METHODS

Open labeled randomized controlled trial was studied at Department of Neonatology, Institute of Child Health (extramural unit) and Institute of Obstetrics and Gynecology (intramural unit) of Madras Medical College, Chennai, Tamilnadu, India. From the year December 2013 to March 2014. Institutional ethical committee approved our study.

The study inclusion criteria includes Haemodynamically stable VLBW neonates weighing between 1000gms-1500gms admitted within 24 hours of birth and excludes: Major congenital malformation, IUGR with abnormal antenatal Doppler, Hypoglycaemia requiring IVF therapy, Need for intra-uterine transfusion.

Sample size was calculated with the hypothesis that starting VLBW babies on full enteral feeding from day one of life with human milk is associated with shorter duration to regain birth weight. To detect a difference 10% between the two groups with 95% confidence (α = 0.05) and 80% power (β = 0.2), the required sample size for the study was 30 in each group.

Babies were stratified into two groups based on birth weight group A (1000-1200 grams) and group B (1200-1500 grams). After getting consent neonates satisfying the inclusion criteria were randomly allocated to receive feed under any of the two protocols as per the randomization sequence obtained after opening the sealed envelope. The computer-generated randomization sequence with blocks of varying size were inside the envelopes to which the investigator was blinded. Total 69 babies was enrolled in the study after randomization.

Data wise 34 babies were in the full enteral feeding group and 35 babies were in standard feeding group. In group A (1000-1200gms) authors had 19 babies and group B (1200-1500gms) 50 babies were included. Consent also obtained for use of the donor human milk from breast milk bank. Donor health, history for lifestyle risks and blood screening tests were assessed similar to blood donor before collection of milk. Donors were educated regarding the hygienic method of milk expression and collection. Both hand expression and electrical milk bumps were used.

Expressed breast milk was pooled into a sterile 150 ml stainless steel containers. From each main container an aliquot of pooled milk is poured into a small container with appropriate label (pilot sample) corresponding to the main container. Pasteurisation (pasteurization method, known as flash-heat method involved heating of milk in a water bath and held for 30 minutes at 62°C) was done. Milk from pilot container was sent for bacterial growth. Pasturised milk in the main containers were rapidly

feezed to -17 degree and then stored till culture report. If bacterial growth detected in the pilot sample pooled milk in the corresponding main container was discarded. Pasteurized, culture negative milk was stored in the freezer with proper labelling including date of collection, pasteurization and culture report with date. Pasteurized, frozen milk was thawed by keeping the container in lukewarm water before giving to babies. Once thawed, milk was used within 4-6 hrs.

Full enteral feeding group: (study group): Babies were started on enteral feeds with human milk at the rate of 60ml/kg/day from day one and progressed by increments of 20 ml/kg/day up to maximum enteral feed of 180 ml/kg/day. Standard feed group (1000-1200 gram): Babies were started with human milk feeds at the rate of 20ml/kg/day on day one along with intravenous fluid of 60 ml/kg/day. (Total fluid 80ml/Kg/day) Enteral feeds were increased by increments of 20 ml/kg/day up to maximum enteral feed of 180 ml/kg/day.

Standard feed group (1200-1500gm Babies were started on human milk feeds at the rate of 40ml/kg/day along with intravenous fluids 40 ml/kg/day from day one. Human milk feeds were increased by 20 ml/kg/day up to maximum enteral feeds of 180 ml/kg/day. Except for the feeding protocol, other managements in two groups were the same as per unit policy. If any troublesome effect was noted in the study group, then the unit protocol was followed till the time of recovery and the feeds were started as in the study group. During the study period the following data were monitored.

It included daily weight measurement, prefeed abdominal girth measurement, gastric aspirate as per protocol, time taken to reach full enteral feedings and fluids intake (both intravenous and enteral feed). Before giving feed, abdominal girth measurement was done at the level of umbilicus. If there was an increase in abdominal girth above 2 cm, then gastric aspiration was done. When gastric aspirate volume was 2-3 ml or less and the clinical condition of the baby is stable, enteral feeds were continued. If the volume of gastric aspirate was 30-50% of pre feed volume or 3ml/Kg, then the volume of human milk feed was not increased over the following 24 hours.

Indications for withholding feed (one or more of the following): If the volume of gastric aspirates was above 50% of feed volume; Minimal blood tinged or coffee ground aspirate; Significant vomiting (bile stained or blood stained); Visible dilated bowel loops ;Abdominal wall erythema or tenderness ; Gross or occult blood in stools. NEC was suspected in infants with abdominal or systemic symptoms and signs and staged as per modified Bell's classification. The primary and secondary outcomes of the trial were analysed in intervention and control groups. Caregivers were not blinded to the randomized allocation, but the personnel involved in analysis were blinded.

RESULTS

Full enteral feeding group infants had lesser days of intravenous fluids compared to babies in the standard feeding group. However, it was not statistically significant. There was no difference in incidence of clinical or culture positive sepsis and duration of hospital stay. None of the babies in our study series developed necrotizing enterocolitis. Full enteral feeding group regained birth weight at a mean age of 17.37±4.9 days and in the standard feeding group, birth weight was regained at a mean age of 19.8±4.3. Babies regained their birth weight two days earlier in full enteral feeding group than standard feeding group and this was not statistically significant. Full enteral feeding group regained birth weight at a mean age of 13.12±2.17 days and in standard feeding group at a mean age of 15.38±3.57. Babies regained their birth weight two days earlier in full enteral feeding group than standard feeding group and this was statistically significant (p - 0.009). Full enteral feeding group babies had lesser number of days of intravenous fluids compared to babies in standard feeding group. It was statistically significant (p - 0.003).

DISCUSSION

This study compared stable VLBW babies who were fed full enteral feeding from day one using human milk with standard feeding group and has shown that, babies achieved earlier regain of birth weight in full enteral feeding. The full enteral feeding regimen was safe with no differences in the incidence of NEC and other feed related morbidities.

Regain of birth weight

Babies in the full enteral feeding group regained their birth weight at 14.18 days compared to 16.33 days (p - 0.028) in the standard feeding group. Sanghvi KP et al study found that babies (1200 -1500 grams) in full enteral feed group regained birth weight (5.52 vs. 12.7 days) 7 days earlier than the babies in their control group.[14] In the 1200-1500 grams babies in our study, regained birth weight at a mean age of 13.1 days in full enteral feeding group and 15.4 days in standard feeding group. The difference was probably because we started human milk at the rate of 60 ml/Kg/day on day one whereas in their starting volume was 80 ml/Kg/day. Feed advancement rate was same in both studies. Other reasons could have been the higher incidence of maternal hypertension (36%), poor antenatal steroid coverage (complete course in 20%) and higher proportion of SGA (16%) in our babies. Previous studies have reported that maternal hypertension increased the time taken to achieve full enteral feeds by 11.2%. The reason could be that the abnormality of the umbilical artery blood flow in utero may continue in the splanchnic circulation even after birth for some days compromising feeding tolerance and full enteral feeding attainment.[15]

Similarly in Wang et al, study, early enteral feeding neonates regained their birth weight at 20 days in the 1000 - 1250 grams group. In our study babies in the 1000 - 1200 grams subgroup regained birth weight by 17 days. This earlier regaining of birth weight in our study could be due to the use of exclusive human milk compared to either breast milk or preterm formula in Wang et al study. Salhotra et al, found that babies in the fast enteral feeding group regained birth weight earlier (median 18 days) after their study of Indian infants.[17] They used only expressed breast milk for enteral feeds. Krishnamurthy S et al, also concluded that VLBW neonates in the rapid advancement group (30ml/kg/day) regained birth weight earlier (median 16 days vs. 22 days) in their study using expressed human milk or formula.[18]

Duration of hospital stay and intravenous fluid

In trial the number of days of hospital stay (19.76 days vs 20.71 days) and the duration of intravenous fluid administration was lesser in the full enteral feed group compared to the standard feed group though not statistically significant. In the randomised trial by Caple et al, comparing slow and rapid feeding volume progression in preterm infants, it was found that babies in the rapid feed advancement group had lesser intravenous fluid days and hospital stay.[19] Similar results were obtained in the study by Karagol B S et al, on comparing slow versus rapid feed advancement in VLBW babies with birth weight 750gms-1250gms.[20] In Sanghvi K P et al, study the number of days in hospital was significantly less in the full enteral feeding group (mean 15.04 days, SD±5.26).[14] But in the control group, the mean duration of hospital stay (mean 28.04 days, SD±6.76) was relatively high when compared to our study where babies in full enteral feed and standard feed groups duration of hospital stay was 19.76 days SD±6.69 and 20.71±7.71 days respectively. Krishnamurthy S et al, while comparing rapid and slow progression of enteral feeding, found a significantly lesser number of IVF days (median 2 days vs. 3.4 days) ($p < 0.001$), and shorter hospital stay (median 9.5 days vs. 11 days) ($p = 0.003$) in the rapid advancement group using either human milk or formula.[18]

Sepsis

There was no statistically significant difference in the incidence of infection between the full enteral feed group (17.64%) and standard feed group (15%). The reason could be earlier the use of human milk in both the groups. Lavole et al, study the early nutrition group reached full enteral nutrition earlier and early initiation of enteral nutrition with human milk had reduced the incidence of CONS associated late onset bacteremia in VLBW infants.[21] Karagol et al, while studying on rapid feed advancement found that the incidence of sepsis (culture positive) was less in the rapid feeding group.[20] Hylander et al, in his study comparing the presence of infection in human milk feed and formula feeds concluded that human milk feeding had reduced odds of infection.[22]

Necrotizing enterocolitis

There was no incidence of NEC in our study. This could be due to the use of exclusive breast milk. Lucas et al, found a 6-10 fold increase in necrotizing enterocolitis in babies receiving formula feeds and a 3 fold increase in those who received formula plus breast milk compared to breast milk only.[23] Pasteurized donor milk is similar to raw maternal milk with regards to the risk of NEC. The Cochrane review by Morgan et al suggested that there was no difference in the risk of NEC between slow and rapid progression of enteral feeds. Sisk et al, wanted to determine if high proportions of (50% or greater) human milk enteral feeding initiated during first 2 weeks of life offered protection against NEC.[24] They concluded that feeding with at least 50% human milk was associated with a six fold reduction in the risk of NEC. This could explain the zero incidence of NEC as both groups in our study group had exclusive human milk feeding. In the study conducted by Leaf et al, in preterm growth restricted infants, there was no difference in the incidence of NEC among those who were fed early or late.[11] In Sanghvi KP et al, study which was done with full enteral feeding from the initial few hours of life, none of the babies developed necrotizing enterocolitis.[14] This was replicated in our study as well. Boo NY et al, studied the risk factor associated with feed intolerance in VLBW babies was due to the delay in starting the first feed and suggested that to promote tolerance, enteral feeds should be started as soon as possible during the first 72h of life.[25]

The strengths of this study

This was a well-designed randomized and controlled trial with adequate sample size. This is one of the few studies done with exclusive breast milk. The breast milk bank in our unit ensured adequate breast milk. The use of a standard feeding protocol and strict adherence to feeding policies helped us in comparing the full enteral feeds with standard protocol.

The limitations of this study was that the donor milk was not classified as term and pre term milk. Hence a difference in the protein and caloric contents might have had an influence on the outcomes; Since different clinicians assessed the feed intolerance and other outcomes there might have been observer bias; Long term neurological outcomes were not studied

Implications for practice

Full enteral feeding can be initiated from day one with standardized feeding guidelines in hemodynamically stable VLBW neonates. The practice provides an encouragement for exclusive breast feeding policy among the care givers and the mothers. If we could collect and

process donar breast milk separately from preterm and term mothers it will be of more use.

Implications for further research

A larger randomized controlled trial with more number of babies would provide us with a better knowledge of the secondary outcomes like duration of hospital stay and incidence of sepsis. The donor milk may be a variable in terms of caloric and protein content. The nutritional components of donor milk may be altered by pasteurization. Hence a study analyzing the nutrient contents of the donor milk would be of more use. Further studies with fortified donor human milk would also provide us additional information. A long term follow up study analyzing the growth and neurodevelopmental outcome would provide us the impetus to use breast milk from day one of life

CONCLUSION

Full enteral feeding from day one of life in hemodynamically stable very low birth weight babies with exclusive human milk (both maternal and donor milk) results in fewer days to regain birth weight. There is also no evidence that full enteral feeding has adverse effects particularly on the risk of necrotizing enterocolitis. We conclude that initiating full enteral feeding practices is an effective, feasible, cost effective and safe intervention. The fear of growth restriction due to inadequate nutrition in this critical period should replace the fear of NEC in implementing nutritional strategies for these babies.

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