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Original Research Paper

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EFFECT OF BREAST MILK ADMINISTERED ORALLY AS MINIMAL ENTERAL NUTRITION PRIOR TO TUBE FEEDING (OMEN) IN PRETERM INFANTS – SINGLE CENTER RANDOMIZED CONTROL TRIAL

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**ABSTRACT** BACKGROUND: Safety and clinical benefits of early Minimum Enteral Nutrition (MEN) have been demonstrated by several trials. MEN is administered as tube feed bypassing the oral phase of digestion. Oropharyngeal administration of colostrum has shown positive trend to achieve feed tolerance. Aims: To study the effect of early initiation and subsequent continuation of minimal oral feeding prior to tube feeds on duration to achieve of full enteral feeds.

**METHODOLOGY: DESIGN:** Open label RCT. **Setting:** Tertiary level care NICU. **Participants:** Hundred preterm very low birth weight neonates with no anomaly. **Intervention:** Infants received 3mL/kg/d of breastmilk or nothing via oral route q2h, beginning within 24-48h of birth which was continued until oral feedings initiated. In both groups tube feeds were introduced (10 ml/kg/d within 24-96 h) & increased (10-20 ml/kg/d) until 180 ml/kg/d. Oral feeding was based on infants cues and a post menstrual age of  $\geq$  32 week or weight  $\geq$  1250 gram. **Outcome: Primary:** Time to reach full tube feeds (days). **Secondary:** NEC, sepsis, mortality, and duration of hospital stay. **Duration:** 1 year.

**RESULTS:** Infants in OMEN group reached full enteral feeds earlier (14.2  $\pm$  9.0 vs 18.8  $\pm$  11.8, p 0.03) and were discharged at relatively younger post menstrual age compared to those in the TMEN group. There was no significant difference in the incidence of NEC, sepsis and mortality.

**CONCLUSION:** Administration of small quantity of human milk orally before each tube feed led to earlier achievement of full volume enteral feeds.

# **KEYWORDS** : Preterm, Human milk, Oropharyngeal, Nutrition.

# INTRODUCTION:

Preterm infants unlike their term counterpart are fed via a naso or orogastric tube that bypasses the oropharynx. Deprivation from benefits of salivary secretion during the oral phase of digestion as well as the immunity conferred by the colostrum make their oral cavities vulnerable for colonization by pathogens (1,2). Oral priming with colostrum was hypothesized to be a better way to strengthen the local immunity. Recent meta-analysis published by Tao et al did not show significant difference in the incidences of NEC, late onset sepsis, and death in preterm infants. However a trend toward a positive effect was observed. Hence oral administration of colostrum (OAC) has been recommended as routine care for preterm infants in the NICU (2). Clinical benefits of trophic feeds (administered through naso or orogastric tubes) have been supported by several RCTs. The benefits have been attributed to altered gastrointestinal disaccharidase activity, hormone release, blood flow, motility, and microbial flora (3,4). We hypothesized orally administered minimal enteral nutrition (MEN) before each tube feed may potentiate the beneficial effects of tube feeds alone resulting in earlier achievement of full tube enteral feeds. Aim of our study was to study the effect of early initiation and subsequent continuation of minimal oral feeding prior to tube feeds on duration to achieve of full enteral feeds.

# METHODOLOGY:

Present study is a prospective open label randomized clinical trial, conducted in a tertiary level neonatal intensive care unit (NICU), designed to evaluate the efficacy of oral administration of expressed breast milk (EBM) prior to each tube feed on the duration the achieve full enteral feeds, NEC,

sepsis and mortality. Institutional ethics committee permission was obtained. Inclusion criteria were preterm (<34 weeks of gestation) and very low birth weight (birth weight <1500g) neonates. Exclusion criteria were – Syndrome, major congenital malformation, post gastrointestinal surgery.

Neonates satisfying inclusion criteria after obtaining parent's consent were enrolled within 1 hour of admission. Eligible neonates were randomized into two groups, using a 1:1 ratio. Random sequence generation was performed by using random allocation software in variable blocks of 2 or 4. Randomization codes were supplied in sequential numbered opaque sealed envelopes. Infants receiving oral plus tube enteral feeds were randomized in oral minimum enteral nutrition (OMEN) group and those receiving only tube feeding were randomized in tube minimal enteral nutrition (TMEN) group.

OMEN group: Infants received 0.2 ml/kg (but not more than 3ml/kg/d) of own mother's milk (OMM) or donor breast milk (DBM) via oropharyngeal administration prior to each tube feed (10ml/kg/d) q2h within first 24 hours of birth. OMEN was continued until infant was started on oral feeding trials. TMEN group (Control) infants received only tube feeds (10ml/kg/d) q2h within 24 hours of birth. Feeding was continued until infants were judged to be ready to tolerate feeds (defined as absence of following any two findings - greenish or altered aspirates, abdominal distention (increase in abdominal girth by 2cm) and absent bowel sounds). Tube feeds were gradually increased (by 10ml/kg/day for Extremely Low Birth Weight (ELBW) infants and 20ml/kg/day for infants weighing >1000 grams and  $\leq$ 1500 grams) based on baby's feeding

tolerance. Full enteral feeds were defined when the infant tolerated volume of 180 to 200 ml/kg/day. Decision of starting oral feeds was taken based on infant's oral cues and either gestation age  $\geq$  32 weeks or weight  $\geq$  1250 grams.

Measurement of outcomes of interest: 1) Time to reach full tube enteral feeds (in days), 2) Necrotizing enterocolitis (confirmed by at least two of the following features: Abdominal radiograph showing pneumatosis intestinalis or gas in the portal venous system or free air in the abdomen or Diagnosis of NEC confirmed at surgery as per current standard protocol in NICU), 3) Growth (Time to regain birth weight and rates of weight gain), 4) Incidence of invasive infection (as determined by culture of bacteria or fungus from blood, cerebrospinal fluid, urine or from a normally sterile body space), 5) Duration of hospital stay in days (As per the NICU policy infants who satisfy following criteria are discharged from NICU (Infants is medically stable on room air for 48 hours with weight >1500 g, consistent weight gain 15 to 20 g/day for 2 consecutive days on oral feeds and mother is confident). Duration of respiratory support during hospital stay was taken as an outcome for the safety of oral administration of milk

A sample size of 100 was based on our records. In our unit the average time taken by an infant with BW  $\leq$  1500 gram to reach full gavage enteral feeds was 15 days. For a difference of 3 d, with an error of 0.05 and power 80%, the estimated sample size 50 in each group. To account for loss to follow up, needed total 111. Data was analyzed by SPPS version 20 software. Categorical variables compared using the chi square or Fisher's exact test. Means of continuous measures between groups compared using two sample independent t test as appropriate. P <0.05 considered significant.

**Data availability:** The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

### **RESULTS:**

Hundred and eleven (111) newborns were included in this study. Out of these, 11 patients could not complete the study due to reasons such as withdrawal of parental consent and voluntary shifting of neonates to different hospital. Thus, data of 100 newborns with 50 in each group was included in the final analysis (Fig. 1). There was no significant difference in baseline demographic characteristics between the study groups (Table 1). Results are summarized in Table 2. Infants in OMEN group reached full enteral feeds earlier (14.2  $\pm$  9.0 vs 18.8  $\pm$  11.8, p 0.03) and were discharged at relatively younger post menstrual age compared to those in the TMEN group. Overall incidence of NEC (6% vs 10%) and blood culture proven sepsis (16% vs 22%) was lower in OMEN group. Duration of NICU stay (days), weight gain (g) at NICU discharge, and duration to achieve full oral feeds (days) did not differ among the groups. Overall duration of respiratory support ( noninvasive / invasive) did not differ significantly between the groups.

### DISCUSSION:

Feeding intolerance is common among preterm infants and may either be a benign sign of reduced GI tract motility or an initial manifestation of NEC. Based on the existing evidence, MEN, otherwise called trophic feeds or gut priming, does not increase the risk of NEC or feeding intolerance (5).

The lipolytic triad – lingual lipase, breast milk, and pancreatic lipases are related to the digestion of dietary fats in infants. Studies have shown the activity and specificity of these enzymes possibly influence micelle formation, intestinal health, breast milk jaundice, and the absorption of other nutrients. In premature infants, the action of lingual and breast milk lipase are particularly important in absorption of dietary fatty acids (6). Thus oral administration of breastmilk may benefit the preterm in multiple ways and not restricted to strengthening immunity. The minimal quantity of 3ml/kg/d was decided arbitrarily based on the experience with different weight babies in NICU.

Similar study published by Mahmoud et al used own mother's milk for oral administration (OPAMM). We administered colostrum, OMM or DBM based on the availability.As observed in study by Mahmoud et al, OMEN did not affect the incidence of NEC, sepsis, and mortality (7). Like in OPAMM study, OMEN showed positive trend towards less episodes of feeding intolerance and shorter duration to reach full gavage feed (7). Infants in OMEN group were discharged at relatively younger age compared to those in TMEN group. The multimodal beneficial effects of OMEN can be attributed to -1) effects of macro, micro and bioactive factors in breastmilk, 2) protective role of saliva and salivary enzymes, 4) it's beneficial impact on neuropsychomotor outcome (1, 8-10).

We acknowledge limitations of our study being pilot single centered trial with small sample size. We were not able to blind oral administration of milk. Additional limitation of our study is that we have only evaluated short-term outcomes, in a selected group of premature infants. We did not analyze effect of OMEN in growth restricted infants. This would significantly affect generalizability of this study. Our study was underpowered to demonstrate differences in secondary outcomes between two intervention drugs.

#### CONCLUSION:

Oral administration of small amount of breast milk before each tube feed leads to achievement of earlier full volume tube feeding and younger gestational age at discharge from NICU.

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