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Original Research Article

Administration colostrum in preventing mortality and morbidity in preterm infants

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ABSTRACT

Background: Oropharyngeal administration of colostrum has found to play a role in preventing the Necrotizing Enterocolitis (NEC), thus reducing mortality and morbidity in preterm infants. We aimed to determine whether early oropharyngeal administration of mother's own colostrum can reduce the rates of NEC and/or mortality in preterm infants.
Methods: We conducted a randomized, placebo controlled, intervention study in Department of Neonatology, Bangabandhu Sheikh Mujib Medical University, Dhaka from 2019 to 2021. Total 92 infants were enrolled, 52 were randomized to oropharyngeal administration of colostrum group and 40 to placebo group. Oropharyngeal administration of colostrum group received maternal colostrum (0.2 ml), after 24 hours of postnatal life and were given every 3 hour for the next 3 days. Serum IgA was measured at 24 hrs and 7th day of postnatal age. Clinical data during hospitalization were collected. SPSS version 21 was used for statistical analysis.
Results: Baseline characteristics were comparable and almost similar between the two groups. There was significant reduction in the incidence of NEC stage 2, 16 (30.7%) vs. 26, (65%); p = 0.001). There was significant reduction of age of achieving full enteral feeding (12.1±4.5 vs 19.5±7.5; p = 0.001), disseminated intravascular coagulation (DIC) 12 (23%) vs. 22 (55%); p=0.002, use of mechanical ventilators, 11 (21.1%) vs. 22 (55%); p = 0.001 and number of inotropes (1.2±0.3 vs. 1.61±0.4975; p = 0.002), duration of inotropes (19.7±14.2 vs. 36.5±17.5; p=0.002) in OAC group. However, there was no significant difference in probable sepsis, culture proven sepsis, survival rate and serum IgA level at 1st and 7th day in OAC group, compared to placebo.
Conclusions: There was a positive effect in decreasing the incidence of NEC, but no significant effect was observed on survival rate. This intervention facilitates faster achievement of full enteral feeding, reducing the risk of DIC in preterm infants.

Keyword: Oropharyngeal administration, Colostrum, Preterm, Necrotizing enterocolitis, RCT

INTRODUCTION

Every year, an estimated 15 million babies are born preterm, and this number is rising. Preterm birth complications are the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths in 2015.[1] Despite the substantial advances in neonatal care, mortality and morbidity remain high in this population Necrotizing enterocolitis (NEC) is major risk factors for mortality and morbidity in premature infants.[2-4] The incidence of NEC is 2-7% among infants with gestational age (GA) < 32 weeks and 5-22% among infants with birthweight

(BW) <1000 g.[5] NEC is a complex process that involves inflammation and bacterial invasion of the immature mucosa. These mechanisms require the concurrent presence of an immature immune system (increased susceptibility) and triggers that lead to dysbiosis (disruption of the normal intestinal bacterial microbiome, resulting in increased growth of potentially pathogenic bacteria) as well as an exaggerated inflammatory host response with the release of cytokines and chemokines.[6-9] Delay to commence enteral feeding are factors that acting synergistically to promote intestinal atrophy and abnormal bacterial colonization of the bowel.[10,11] Despite a variety of infection control measures and the use of antibiotics, preterm infants remain at high risk of infection and NEC, both of which are associated with poor growth and neurodevelopmental outcomes.[12] They are also linked to prolonged hospital stays and substantial increases in the cost of care, both to hospitals and families.[13,14] Oropharyngeal colostrum can be a continuation of the exposure of the fetal oropharynx to the growth and protective biofactors of the amniotic fluid during fetal life. Colostrum, the fluid secreted by the mammary glands in the first few postnatal days, is rich in biological protective factors, present in a high concentration in the colostrum of mothers who have delivered preterm infants. Colostrum may act via different mechanisms: as a local barrier that prevents adhesion of microbes to the mucosa, facilitating the absorption of immune factors by the buccal mucosa, prebiotic and anti-inflammatory actions and antioxidant properties of lactoferrin and by the stimulation of intestinal growth and repair.[10] In addition to being absorbed by the intestinal tract, these immunoactive factors can also produce specific benefits through oropharyngeal contact by "per oral breast milk feed", which may promote immunocompetence by mechanisms of immunomodulation of cells within the oropharyngeal-associated lymphoid tissue (OFALT) and gut-associated lymphoid tissue (GALT) systems, and the mucosal absorption of factors that interfere with bacterial colonization.[15] Transforming growth factor-β (TGF-β) is an anti-inflammatory cytokine found in human colostrum.TGF-β is also responsible for the antibodies produced by B-lymphocytes' class-switching, in particular, secretory immunoglobulin A (IgA). Japanese researchers found a correlation between the TGF-β1 concentration in human milk and IgA levels in the infant serum.[10-16] IgA secretion in human milk is vital to provide passive immune protection, as the new-born infant is unable to synthesize antibodies until 30 days postpartum.[17] There are few studies available to assess the protective role of buccal colostrum on preventing mortality and morbidity in preterm infants. The objective of this study was to determine if early (within the first 72 hours of life) oropharyngeal administration of mother's own colostrum can reduce rates of NEC, and/or mortality in preterm infants and to evaluate the production of bioactive proteins after activation of oropharyngeal mucosa-associated lymphoid tissue (MALT) and systemic circulation, we had measured the concentrations of immunologic factors (serum IgA) in blood.

METHODS

Study design

We undertook a randomized, placebo controlled, intervention study in the Department of Neonatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, from July 2019 to June 2021, after getting the approval from the Institutional Review Board.

Eligibility criteria

All inborn preterm neonates gestational age <34 weeks and birth weight ≤1800 g satisfying the eligibility and exclusion criteria were enrolled in the study. Infants with gross congenital anomalies, any surgical condition where there is contraindication of breast milk, contraindication of providing breast milk were excluded from the study. According to Helsinki Declaration for Medical Research involving Human Subjects 1964, all the parents were informed about the study design, the right of the participants to withdraw themselves from the research at any time, for any reason. Informed written consent were obtained from parents who voluntarily provided consent to participate in this study.

Data collection procedures

Face-to-face interview with the mother or caregivers were taken to all enrolled neonates. Information regarding demographic and socioeconomic status, date of admission, mode and place of delivery, gestational age, birth weight, maternal history of (PROM), antenatal corticosteroid, antibiotics used etc were recorded. After informed parental consent, regardless of twin or higher-order multiples, each neonate was randomly assigned independently to the colostrum or standard care group. The feeding status of each patient was decided by the attending physicians under the principle that trophic feeding should be started as soon as possible if there is no contraindication (eg, bilious gastric residual, fixed dilated bowel loop on radiograph, severe hemodynamic instability). Both groups of neonates was fed fresh mother's own milk. Investigators had met the mothers of each enrolled neonate within 24 hours of delivery and educated them about hand-expression and pumping of breast milk every 2 to 3 hours. Mothers was given prelabelled sterile milk container and instructed to collect their colostrum by using a sanitary hand-expression method and then to send the colostrum to the NICU .1c.c disposable syringes was used to administer colostrum via the oropharyngeal route.

Between 24-48 hrs after birth, each neonate received 0.2 ml of his or her mother's colostrum (0.1 ml in each buccal mucosa) every 3 hours for 72 consecutive hours, regardless of whether the infant was fed enterally. One syringe was placed on the patient's right or left buccal mucosa, and the colostrum was administered toward the posterior oropharynx for at least 10 seconds. The same

process was repeated on the opposite site. Heart rate (HR), respiratory rate (RR), blood pressure, and pulse oxygen saturation (SpO2) was recorded immediately before and after every intervention session. Session was plannned to discontinue if any of the following issues was developed: requirement of an increase in fraction of inspiratory oxygen 0.1 to maintain SpO2 between 90-95%, bradycardia (HR,100/minute) or tachycardia (HR 200/minute), and tachypnea (RR 80/minute). Other group received only standard care.

Serum IgA was measured at 24 hrs of birth before applying colostrum and 7th day of age. The incidence of NEC, and other inflammatory medical comorbidities of prematurity, such as bronchopulmonary dysplasia (BPD), ventilator-associated pneumonia (VAP), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), clinical, probable and proven sepsis, time to reach full feeding (100 ml/kg/day) and mortality were documented in the hospital case record form. NEC was diagnosed by clinical and radiological evidence. Relevant data from history, physical examination and investigations was recorded in predesigned questionnaire. Data of pregnancy including number of fetuses, use of antenatal corticosteroids or antenatal antibiotics and presence of PROM were recorded. clinical data of the newborn including gestational age, birth weight, Apgar score, weight and postnatal age at the onset of sepsis, heart rate, blood pressure, CRT, temperature and origin of sepsis were also recorded. We also collected biological and bacteriologic data included blood cell count, CRP, glycaemia, minimal blood pH and pathogen. At the time of discharge/death following data was recorded: duration of NICU stay, duration of mechanical ventilation, number and duration of inotropes/vasopressor required. Primary outcome variables were NEC stage 2, survival rate, serum IgA level at 1st and 7th day.

Operational definition

Ventilator associated pneumonia defined as clinical signs of pneumonia combined with pneumonic infiltration on 2 serial chest radiographs in patients receiving mechanical ventilation for 48 hours. Clinical signs of pneumonia included worsening gas exchange, increased oxygen requirements, increased ventilator demand, and clinical symptoms (new onset of purulent sputum, temperature instability, leukopenia/leukocytosis with left shift, apnea/ tachypnea, or bradycardia/ tachycardia). Clinical sepsis was defined as clinical signs of infection accompanied by concurrent antibiotic treatment for 3 days. Clinical signs of infection included all 3 of the following categories and at least 1 sign in each of the 3 categories: general signs (fever, apnea/tachypnea, respiratory distress, positive fluid balance), laboratory results (leukopenia/leukocytosis, increased C-reactive protein), and hemodynamic alterations (hypotension, tachycardia, altered skin perfusion, decreased urine output, increased base deficit). Probable Sepsis was defined as presence of signs and symptoms of infection and at least two abnormal laboratory results when blood culture is negative Proven sepsis was defined as bacterial growth in at least 1 blood culture and fulfillment of clinical sepsis. Vital signs was monitored throughout the study and any occurrence of adverse events recorded. Clinical data from each patient's hospitalization was collected at discharge from the NICU. All patients was managed as per standard clinical guidelines for management of septic shock in neonates. The management includes appropriate fluid resuscitation, use of inotropes/vasopressors, antibiotics and blood component transfusion.

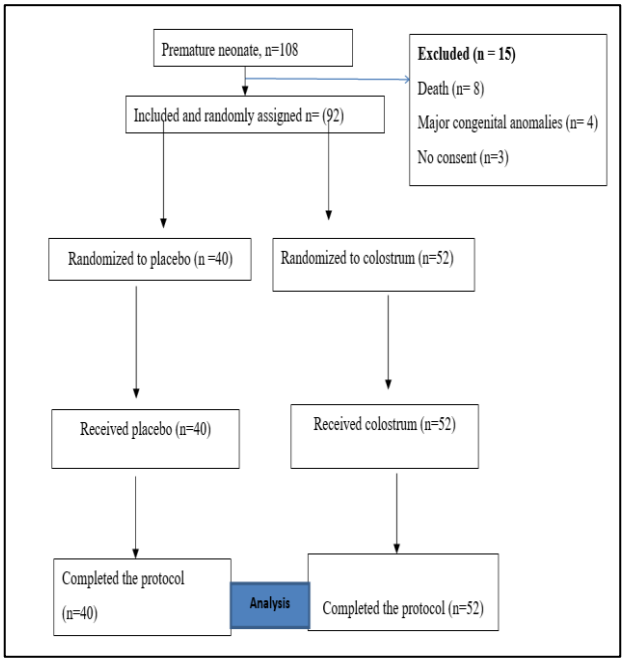

Figure 1: Consort flow diagram for study.

Power and sample size calculation

This RCT is efficacy-based with sample size determined for the primary outcome measure, and is designed to avoid local contamination effects. Power calculations rely on a 40% reduction in the incidence of NEC, with a design effect of 1.01. similar to the reduction in NEC observed in a study. Using a significance level of 10%, a power of 80% results in a preliminary sample size of 92 infant cases were required for the intervention and control group. Among total 92 infants were enrolled, 52 were randomized to OAC group and 40 to placebo group.

Data analysis

Data were analyzed using the statistical package for social sciences (SPSS) version 21. Quantitative data was expressed as mean±SD and categorical data was presented as proportion. All quantitative variables (between the groups of survivors and non-survivors) was compared by unpaired t test; categorical variables was compared by Chi-square test or Fisher's exact test $p<0.05$ was considered as significant.

RESULTS

Total 108 preterm neonates below 34 weeks were enrolled in this study (Figure 1). Among them 15 newborn were excluded. 8 was died, 4 newborn had major congenital malformations, and 3 parents did not give consent. Finally, out of 92 preterm newborns, 52 were randomized to colostrum group and 40 were randomized to placebo group. All the newborns were randomized to OAC and placebo group in this study. Maternal and neonatal general characteristics of the enrolled participants are shown in (Tables 1-2).

Table 1: Baseline characteristics of maternal factors (n=92).

Characteristics	OAC (N=52) Frequency (%)	Placebo (N=40) Frequency (%)	P value
Maternal age (years)			
<20	4 (7.6)	0	0.063
20-30	40 (76.9)	29 (72.5)	
31-39	8 (15.3)	8 (20)	
>40	0	3	
Maternal education			
Less than high school	3 (5.7)	2 (5)	0.985
High school	21 (40.3)	16 (40)	
Degree or equivalent	28 (53.8)	22 (55)	
Parity			
Primipara	24 (46.1)	11 (27.5)	0.068
Multipara	28 (53.8)	29 (72.5)	
Regular antenatal visits			
<4	3 (5.7)	5 (12.5)	0.26
>4	49 (94.2)	34 (85)	
Maternal DM	7 (13.4)	5 (12.5)	0.892
Maternal HTN			0.727
Yes	24 (46.1)	17 (42.5)	
Antenatal corticosteroid			
None	1 (1.9)	2 (5)	0.681
Incomplete dose	2 (3.8)	2 (5)	
Complete dose	49 (94.2)	36 (90)	
PROM>18 hrs			
Yes	12 (23.07)	13 (32.5)	0.314
No			
Antenatal antibiotics			0.314
Yes	12 (23.07)	13 (32.5)	

Qualitative data are presented as the number and percentage, Statistical test: Chi-square test for categorical data, p<0.05 were considered as significant. ns-not significant

Baseline characteristics were mostly comparable between the two groups. There was no extremely premature baby (<28 weeks) in the OAC colostrum group. Gestational age for most of the preterm babies gestational age was >28 weeks both in the OAC (100%) and placebo group (87.5%). Birth weight was weighed >1000 gram in both the groups, that is stands for 98% in colostrum OAC group and 82.5% in placebo group.

Table 2: Baseline characteristics of neonates (n=92).

Characteristics	OAC (N=52) Frequency (%)	Placebo (N=40) Frequency (%)	P value
GA (weeks)			
<28	0	5 (12.5)	0.009
>28	52 (100)	35 (87.5)	
Birth weight (Grams)			0.009
<1000	1 (1.9)	7 (17.5)	
>1000	51 (98)	33 (82.5)	
Fetal growth			
SGA	6 (11.5)	10 (25)	0.113
AGA	46 (88.4)	29 (72.5)	
LGA	0	1 (2.5)	
Sex			
Male	31 (59.6)	19 (47.5)	0.304
Female	20 (38.4)	21 (52.5)	
Mode of delivery			
LUCS	47 (90.3)	31 (77.5)	0.94
NVD	4 (9.7)	9 (22.5)	
APGAR score at 1st min			
>7	49 (94.2)	37 (92.5)	0.739
6-Apr	3 (5.7)	3 (7.5)	
APGAR score at 5th min			
>7	52 (100)	40 (100)	0.739
6-Apr	0	0	

Qualitative data are presented as the number and percentage, Statistical test: Chi-square test for categorical data, p<0.05 were considered as significant. ns-not significant

Most of the babies were AGA in both the groups. In colostrum OAC group 11.5% was SGA and in placebo group 25% was SGA. Most of the infants were born by LUCS 78 (84%). We found the APGAR score at 1st min was >7 for 93.4% of babies. A comparison of the clinical outcome between the OAC and control groups is shown in (Table 3). There was significant reduction in the incidence of NEC stage 2, 16 (30.7%) vs. 26 (65%); p = 0.001 and NEC stage 3 was not found in enrolled patient. There was no statistically significant difference in survival rate between the two groups. Among the secondary outcome there was significant reduction of DIC, 12 (23%) vs. 22 (55%); p=0.002, age of achieving full enteral feeding (12.10±4.568 vs 19.55±7.594; p=0.001), There were no statistical differences on the incidence of shock, Intraventricular haemorrhage, ventilator-associated pneumonia, BPD, ROP that were needed for laser treatment, AKI duration of NICU between the two groups. The comparison of treatment outcome between OAC and control group is shown in (Table 4). The use of mechanical ventilators 11 (21.1%) vs. 22 (55%); p=0.001 and no of inotropes (1.18±0.395vs 1.61±0.497; p=0.002), duration of inotropes (19.77±14.249 vs. 36.57±17.502; p=0.002)

was found less in OAC group compared to control group and these were statistically significant. However, there were no statistical differences on use of CPAP, fluid boluses, and duration of mechanical ventilator between the two groups. There was no statistically significant difference in serum IgA level at 1st and 7th day between the OAC and control groups is shown in (Table 5).

Table 3: Clinical outcomes between the colostrum group and control group at the time of discharge.

Characteristics	OAC (N=52) Frequency (%)	Placebo (N=40) Frequency (%)	P value
NEC stage 2	16 (30.7)	26 (65)	0.001
Ventilator associated pneumonia	4 (7.7)	10 (25)	0.022
BPD	0	2 (5)	0.103
IVH	23 (44.2)	18 (45)	0.941
ROP needed Laser	10 (19.2)	15 (37.5)	0.51
Shock	22 (42.3)	27 (67.5)	0.016
AKI	11 (21.1)	18 (45)	0.015
DIC	12 (23)	22 (55)	0.002
Age of achieving full enteral feeding (d), mean±SD	12.10±4.568	19.55±7.594	0.001
Duration of NICU (d), mean±SD	14.33±5.067	16.30±7.240	0.128
Survived	47	30	0.048

Qualitative data are presented as the number and percentage, Statistical test: Chi-square test for categorical data, p<0.05 were considered as significant. ns-not significant

DISCUSSION

This single-center, RCT showed a potential lower incidence of late-onset sepsis and NEC (Bell stage 2) in preterm infants with GA ≤ 34 weeks who received an OAC intervention. In addition, the incidence of DIC was lower and the time to achieve full enteral feeding was shorter in the OAC group. We also found that the need for MV, number and duration of inotrope was reduced in OAC group compared to the control group. In the published literature, it has been mentioned that OAC could be applied for 5 days after birth or longer, even extending until the baby could receive partial oral feed or reach the correct GA at 32 weeks.[10] Colostrum from the infants' own mothers was selected in our study, and we found that provision of OAC for the 3 days were beneficial for these preterm infants. In our study, we were consistent to administer 0.2 ml of fresh colostrum in buccal mucosa (0.1 ml in each buccal mucosa for 2-min) every 3 hrly for 72 hours for the OAC. This practice probably enabled us to reduce treatment variation that may occur due to OAC procedures. We are aware that wide variations in the OAC procedure, including variation in the dosage of colostrum administered (ranging from 0.1 ml to to 1.0 ml), the duration of each administration (described as "drop into the oral mucosa" or apply for less than 5 sec), the frequency of treatments for each day (every 2 to 6 hours), the duration of the treatment protocol (ranging from 2 to 7 days, or on depending on an as-needed basis), the type of applicator (use of either syringe or swab), and the type of breast milk (use of either fresh or frozen breast milk), have been reported in the published literature.[10,18-20]

Table 4: Comparison of treatment modalities between colostrum and placebo group (n=92).

Treatment modalities	OAC (N=52) Frequency (%)	Placebo (N=40) Frequency (%)	P value
Fluid bolus for shock			
One	19 (36.5)	25 (62.5)	0.752
>one	3 (5.7)	3 (7.5)	
Mechanical ventilator	11 (21.1)	22 (55)	0.001
Duration of MV (hrs) mean±SD	5±1.732	14.91±13.291	0.02
CPAP	20 (38.4%)	22 (55%)	0.504
Inotrope use (number) mean±SD	1.18±0.395	1.61±0.497	0.002
Inotrope duration (hrs) mean±SD	19.77±14.249	36.57±17.502	0.001

Qualitative data are presented as the number and percentage, Statistical test: Chi-square test for categorical data, p<0.05 were considered as significant. ns-not significant

This sort of reported variations or approaches might lead to the inactivation of some immune protective factors, which may result in decreased levels of active substances. However, contamination might also occur, as some studies have shown pathogenic organisms in mother milk samples.[22-25] OAC may be considered a safe procedure in the NICU for preterm infants. We are claiming this as no adverse reactions were observed in either group including oral mucosal damage, apnea, bradycardia, tachycardia or desaturation in our study. It was also applicable for, even in the ELBW infants and sicker infants who required mechanical ventilation within the first 48 hours of life. Our results showed that the incidence of NEC in the OAC group was lower for preterm infants with GA ≤ 34 weeks. These results are consistent with results of a previous study conducted by Yang et al which also reported the incidence of NEC was found to be decreased among the colostrum group.[25] From the theoretical point of view, NEC and LOS are not single-factor diseases and might be triggered and influenced by multiple factors such as the status of preterm infants, the quantity of therapy received and the underlying medical condition, which are all significant contributors.[26]

Table 5: Comparison of serum IgA level between colostrum and placebo group (n=92).

Characteristics	OAC (N=52) Frequency (%)	Placebo (N=40) Frequency (%)	P value
Serum IgA 1st day (Mean±SD)	0.2884±0.12536	0.2683±0.5460	0.346
Serum IgA 7th day (Mean±SD)	3.8317±17.102	0.2997±0.09303	0.195

Evidences suggest that pathogenic colonization of the preterm gut appears to be a primary step in the pathogenesis of both LNOS and NEC.[27,28-31] A pathogen-predominant microbiota promotes injury to the mucosal barrier and facilitates bacterial translocation from the gut into the bloodstream.[22] It is well known that milk biofactors protect against LNOS and NEC, because of their ability to provide antimicrobial, anti-inflammatory and immunomodulatory functions, inhibit pathogen adhesion to the gastrointestinal mucosa, enhance gastrointestinal microbiota, maintain the integrity of the intestinal barrier and repair areas of injury, promote intestinal maturation and motility, and provide antioxidant protection.[32-56] Our findings are in-line with a growing collection of evidence that suggests OAC care is safe and feasible in among VLBW infants.[39,57] Recently, investigators have described improvements to several nutritional outcomes for VLBW infants because of OAC application or a standardized feeding protocol that includes OAC care.[37,39] Specifically, reports have shown that these infants more often receive breast milk for their first feedings, may begin enteral feeds earlier, and may reach full feeds (100-150 ml/kg/day) more quickly. Many studies indicate that OAC may also have the advantages of shortening the time to for achieving full enteral feeding and full oral feeding, reducing the incidence of feeding intolerance, increasing the body weight at the correct gestational age of 36 weeks, reducing the length of hospital stay, and prolonging the duration of breast milk feed.[29,38-51] In our study, it was also observed that the time to achieve full enteral feeding was shorter in the OAC group, which may pose a great significance for the management of premature infants. Abd-Elgawad et al and Sharma et al reported the similar findings.[48,49] One of the most possible mechanisms might be that OAC tends to stimulates oropharyngeal receptors, which consequently improves the motility, secretory and absorptive abilities of the gastrointestinal tract.

Limitations

A potential limitation of our approach is that we did not consider long term follow up. Our study was also monocentric and we did not consider adequate power in calculating the sample size due to COVID-19 pandemic situation.

CONCLUSION

We demonstrated that OAC can be used as a simple and feasible procedure without any additional risk to preterm infants. There is a positive effort in decreasing the incidence of NEC, survival rate, duration of stay in NICU, serum IgA at 1st and 7th day. This intervention may facilitate greater achievement of full enteral feeding, reduce the risk of DIC, use of MV, duration of inotropes in preterm infants, including very preterm and very low birth weight baby.

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