BREASTFEEDING MEDICINE
Volume 8, Number 6, 2013

DOI: 10.1089/bfm.2013.0025

Early Administration of Oropharyngeal Colostrum to Extremely Low Birth Weight Infants

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Abstract

Background: Human milk reduces morbidities in extremely low birth weight (ELBW) infants. However, clinical instability often precludes ELBW infants from receiving early enteral feeds. This study compared clinical outcomes before and after implementing an oropharyngeal colostrum (COL) protocol in a cohort of inborn (born at our facility) ELBW infants.

Study Design: This is a retrospective cohort study of inborn ELBW infants admitted to the Duke Intensive Care Nursery from January 2007 to September 2011. In November 2010, we initiated a COL protocol for infants not enterally fed whose mothers were providing breastmilk. Infants received 0.1 mL of fresh COL to each cheek every 4 hours for 5 days beginning in the first 48 postnatal hours. We assessed demographics, diagnoses, feeding history, and mortality and for the presence of medical necrotizing enterocolitis (NEC), surgical NEC, and spontaneous perforation. Between-group comparisons were made using Fisher's exact test or Wilcoxon rank sum testing where appropriate.

Results: Of the 369 infants included, 280 (76%) were born prior to the COL protocol (Pre-COL Cohort [PCC]), and 89 (24%) were born after (COL Cohort [CC]). Mortality and the percentage of infants with surgical NEC and spontaneous perforations were statistically similar between the groups. The CC weighed an average (interquartile range) of 1,666 (1,399, 1,940) g at 36 weeks versus 1,380 (1,190, 1,650) g for the PCC ($p < 0.001$). In a multivariable analysis with birth weight as a covariable, weight at 36 weeks was significantly greater (37 g; $p < 0.01$).

Conclusions: Initiating oropharyngeal COL in ELBW infants in the first 2 postnatal days appears feasible and safe and may be nutritionally beneficial. Further research is needed to determine if early COL administration reduces neonatal morbidity and mortality.

Introduction

The American Academy of Pediatrics recommends human milk as the preferred nutritional choice for extremely low birth weight (ELBW) (birth weight <1,000 g) infants.[1–3] In addition to the nutritional benefits, decreased rates of necrotizing enterocolitis (NEC),[4,5] NEC or death,[5] retinopathy of prematurity,[6] and sepsis,[7] improved long-term neurodevelopmental outcomes,[8,9] and fewer rehospitalizations[9] after initial discharge have been reported in human milk-fed premature infants.

Human milk contains various antimicrobial factors and immunologically active mediators that are beneficial to premature infants given their immune deficiency and clinical instability.[10–15] The differences in concentrations of some immune mediators between maternal milk and bovine milk[15] and preterm maternal milk and term maternal milk have been well studied.[10–14] Preterm milk contains lower levels of proinflammatory cytokines and higher levels of anti-inflammatory cytokines compared with milk from mothers who delivered at term.[13] The level of immunoglobulin A in preterm milk is higher compared with term milk.[12] On the other hand, the literature is conflicting, and some studies report lower levels of cytokines in preterm milk[11] or equivalent levels compared with term milk.[10] Colostrum (COL) has also been found to contain several immune factors (lysozyme,[16] immunoglobulin,[16] and cytokines[17]) and, in some instances, higher concentrations than in mature milk produced further from parturition.[11,18]

One prior study demonstrated the feasibility and safety of administering oropharyngeal COL to five ELBW infants.[19]

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Based on the immune properties of COL and the potential reduction of infectious neonatal complications, we aimed to determine the clinical impact of implementing a universal oropharyngeal COL protocol in ELBW infants in our intensive care nursery (ICN).

Subjects and Methods

We conducted a retrospective cohort study of all inborn (born at our facility) ELBW infants admitted from January 2007 to September 2011. In November 2010, the Duke ICN initiated a protocol for oropharyngeal administration of COL to infants not enterally fed whose mothers were providing breastmilk. Mothers were instructed on how to use a Medela Symphony® Preemie+™ breast pump (Medela, Inc., McHenry, IL) and collect their COL in sterile specimen containers. The containers were labeled with the infant's name, history number, and date and time of the pumping. Doses (0.2 mL) of COL are drawn up in 1-mL syringes and given to the infant oropharyngeally in the order that it was produced. Small expressed drops of COL were diluted with 1–2 mL of sterile water to remove the drops from the pump collection kit. Infants received 0.1 mL of fresh COL applied to the buccal mucosa via syringe every 4 hours for 5 days beginning in the first 48 postnatal hours when mother's COL was available.

We examined medical records, including demographics, diagnoses, feeding history, length of stay, morbidities, and mortality. Morbidities included medical NEC (Bell stage IIA),[20] surgical NEC, and spontaneous perforation. Between-group comparisons were made using Fisher's exact or Wilcoxon rank sum tests where appropriate. Linear regression was used to determine whether oropharyngeal COL was associated with increased weight at 36 weeks postmenstrual age controlling for gestational age at birth and birth weight. The Duke ICN standardized feeding protocols and parenteral nutrition practices did not change during the period studied (Appendix).

Infants who were born prior to the start of the COL protocol were classified as the Pre-COL Cohort (PCC), and all consecutive infants born after the protocol was initiated were classified as the COL Cohort (CC). Because our intention was to institute a universal oropharyngeal COL protocol, infants born after protocol implementation were classified as CC even if they did not receive oropharyngeal COL.

Statistical analyses of the data were completed using Stata version 11 (StataCorp., College Station, TX). Statistical significance was defined as $p < 0.05$. The Duke University Medical Center Institutional Review Board approved this study.

Results

We identified 369 infants for the study: 280 (76%) in the PCC and 89 (24%) in the CC (Table 1). Seventy-six (85%) of the infants born after protocol implementation received COL. Thirteen of the CC did not receive colostrum: three died on the first day of life, one was never fed, six were started on maternal milk but oropharyngeal COL administration was not documented, and three mothers chose not provide COL/maternal milk. The gestational age, race, gender, 5-minute Apgar score, and length of stay were similar between the two cohorts (Table 1). The CC weighed more at birth compared with the PCC (Table 1) ($p = 0.004$).

Table 1. Demographics of the Study Population

	Pre-colostrum protocol (n = *280*)	*Colostrum protocol* (n = *89*)	p
Gestational age (weeks)	25 (24, 27)	26 (25, 27)	0.22
Birth weight (g)	750 (628, 860)	820 (700, 910)	0.004
Race			0.71
White	100 (36%)	39 (44%)	
Non-white	180 (64%)	55 (62%)	
Male	144 (51%)	39 (44%)	0.23
Apgar score at 5 minutes	7 (6, 8)	7 (6, 8)	0.82
Length of stay (days)	69 (37, 109)	79 (48, 125)	0.14

Data are median (interquartile range) values.

The CC began enteral feeds and regained birth weight earlier than the PCC (Table 2). At 36 weeks, the CC weighed more than the PCC (Table 2) ($p < 0.001$). In a multivariable analysis, COL use was associated with greater weight at 36 weeks adjusted age after correcting for gestational age at birth (+240 g; $p < 0.01$). In a multivariable analysis COL was associated with a greater weight at 36 weeks adjusted after correcting for birth weight (+37 g; $p < 0.01$).

During their postnatal courses, the CC and PCC had similar incidences of medical NEC, surgical NEC, spontaneous perforations, and mortality (Table 3).

Discussion

There are strong theoretical data supporting the use of human milk and COL as a rich source of cytokines, growth factors, and immunologically active chemicals.[11,18] Based on the theoretical potential for benefit from these factors on reduction of infection and NEC, we instituted a universal program to support mothers' ability to provide COL to all ELBW infants regardless of clinical condition and a protocol to guide administration. Furthermore, the clinical outcomes of the CC suggest a nutritional benefit.

Mechanisms for the potential benefit and the trend toward reduced mortality include direct effects of exposure to the wide assortment of cytokines and growth factors found in colostrum. Cytokines such as those found in human COL may be absorbed by the lymphoid immune cells within the

Table 2. Nutritional Outcomes of the Study Population

	Pre-colostrum protocol (n = *280*)	*Colostrum protocol* (n = *89*)	p
Day feedings began	6 (3, 11)	4 (2, 6)	< 0.001
Day reached 100 mL/kg/day of feeds	29 (19, 40)	25 (17, 34)	0.09
Day regained birth weight	15 (11, 23)	14 (11, 19)	0.21
Weight at 36 weeks (g)	1,380 (1,190, 1,650)	1,666 (1,399, 1,940)	< 0.001

Data are median (interquartile range) values.

Table 3. Morbidity and Mortality

	Pre-colostrum protocol (n = 280)	*Colostrum protocol (n = 89)*	p
Medical NEC	17 (6%)	6 (7%)	0.80
Surgical abdominal pathology	44 (16%)	14 (16%)	0.86
Surgical NEC	19 (7%)	4 (4%)	0.62
SIP	25 (10%)	10 (11%)	0.53
Death	55 (20%)	13 (15%)	0.35

NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation.

mucosa-associated lymphoid tissue found in the oropharyngeal cavity.[21–23] Prior authors have reported the presence of immune-modulating chemicals and growth factors within breastmilk and COL. Lactoferrin,[12,14,24] lysozyme,[16] immunoglobulin,[14–16,25] interleukin (IL)-1β,[11,13,17] IL-2,[11] IL-6,[11,13,17] IL-8,[11,13,17] IL-10,[10,13,17] IL-13,[13] epidermal growth factor,[26] tumor necrosis factor-α,[11,13,17] and transforming growth factor-α[26] are a few examples reported in the literature. Compared with term mother's milk, preterm mother's milk has fewer pro-inflammatory mediators (IL-1β, IL-6, IL-8, and tumor necrosis factor-α) and more anti-inflammatory cytokines (IL-10 and IL-13).[13]

Levels of growth factors are higher in COL than in transitional or mature milk. In particular, the epidermal growth factor level is higher in colostrum obtained from mothers who deliver preterm than those who deliver at term.[18] Early administration of human milk may provide an important defense in the developing neonate by facilitating balance of the body's inflammatory reaction to foreign stimuli and enhanced intestinal growth. This inflammatory modulation and improved growth may partially explain the reported decreased rates of NEC,[4,5] NEC or death,[5] retinopathy of prematurity,[6] and sepsis[7] with human milk. Improved long-term neurodevelopmental outcomes[8,9] in human milk-fed infants may be a secondary effect of the components of milk or a benefit of those factors reducing risk of morbidities that contribute to risk of poor outcome.[27,28] Although the definitive mechanism for why human milk results in fewer neonatal complications is unknown, it is plausible that the various immunologically active and antibacterial substances found in human milk and COL play a role in the protection from common neonatal morbidities. Early administration of oropharyngeal COL to ELBW infants may facilitate early exposure to immune modulators and enable the critically ill neonate to realize the various immunogenic benefits.

This study demonstrates a nutritional advantage of early administration of colostrum. The CC began feeds earlier, trended toward reaching full enteral nutrition sooner, and weighed more at 36 weeks post-conceptual age. The reason the CC began feeds earlier is possibly related to a culture shift in the unit. Once the COL protocol began, nutrition and enteral feedings were mentioned more consistently on rounds, and providers were less hesitant to start enteral feeds given that the ELBW infants were already receiving oropharyngeal COL. We were surprised to note significantly higher weights in the CC at 36 weeks adjusted age. The impact may be in part from earlier enteral feeds, although time to full volume feeds was statistically the same. It may be that early COL exposure led to enhanced intestinal surface absorptive function, a possible side effect of earlier exposure to growth factors such as EGF.[18]

The strengths of this study include the comprehensive dataset analyzed for each baby and the fact that the infants were from a single center, limiting the treatment center variability known to occur and affect outcomes. It is the largest cohort of ELBW infants reported to date to have received oropharyngeal COL. Weaknesses include the lower birth weight for the PCC compared with the CC, which may bias the morbidity data against finding a difference between the cohorts. Differences in other aspects of care in the two eras, PCC and CC, are also potentially important. Our dataset was limited by including only gastrointestinal morbidities and did not include retinopathy of prematurity, sepsis, and neurodevelopmental follow-up. These data do not show a decreased rate of gastrointestinal pathologies, which may be expected if the immunoactive substances from COL influence the neonate's developing immune system and is related to the pathophysiology of these common neonatal morbidities. This may be related to the relatively small sample size of 369 infants in the study.

Conclusions

Initiating oropharyngeal COL within the first 2 postnatal days in a group of ELBW infants is feasible and safe and is nutritionally beneficial. Further research is needed to characterize biologic mechanisms and determine if early COL administration can improve ELBW infant outcomes and growth.

Acknowledgments

J.K.S. received support from multidisciplinary training grant HD043728. C.M.C. received support from grant 5U10HD040492-10 from the Eunice Kennedy Shriver Neonatal Research Network, National Institute of Child Health and Development. P.B.S. received support from grant 1K23HD060040-01 from the National Institute of Child Health and Development and grant 1R18AE000028-01 from the Department of Health and Human Services. Support was also received from the Jean and George W. Brumley, Jr., Neonatal-Perinatal Research Institute.

Disclosure Statement

No competing financial interests exist.

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(*Appendix follows* →)

Appendix

Table A1. Extremely Low Birth Weight Enteral Feeding Progression

Colostrum feeding steps	*Caloric density of HM or PF (kcal/ounce)*	*Daily volume*	*Feeding interval*	*Comments*
Step 1	20	10 mL/kg × 120 hours[a]	Every 6 hours	
Step 2	20	↑ 20 mL/kg × 24 hours	2 hours on; 2 hours off	
Step 3	20	↑ 30 mL/kg × 12 hours ↑ 40 mL/kg × 12 hours	2 hours on; 2 hours off	
Step 4	20	↑ 50 mL/kg × 12 hours ↑ 60 mL/kg × 12 hours	2 hours on; 2 hours off	
Step 5	20	↑ 70 mL/kg × 12 hours ↑ 80 mL/kg × 12 hours	2 hours on; 2 hours off	
Step 6	22	80 mL/kg × 24 hours	2 hours on; 2 hours off	Add 1 packet of HMF/50 mL of HM; change to 22 kcal/ounce of PF
Step 7	22	↑ 90 mL/kg × 12 hours ↑ 100 mL/kg × 12 hours	2 hours on; 2 hours off	
Step 8	24	100 mL/kg × 24 hours	2 hours on; 2 hours off	Add 2 packets of HMF/50 mL of HM; change to 24 kcal/ounce of PF
Step 9	24	↑ 110 mL/kg × 12 hours ↑ 120 mL/kg × 12 hours	2 hours on; 2 hours off	Reassess TPN
Step 10	24	↑ 130 mL/kg × 12 hours ↑ 140 mL/kg × 12 hours	2 hours on; 2 hours off	
Step 11	24	↑ 150 mL/kg × 12 hours	2 hours on; 2 hours off	
Step 12	25[b]	150 mL/kg × 24 hours[c]	2 hours on; 2 hours off	Add ¼ teaspoon of protein supplement/50 mL to HM

Some patients may require an individualized feeding plan depending on medical condition and nutritional needs.
[a]120 hours if birth weight <750 g; 72 hours if birth weight 751–1,000 g.
[b]Additional kcals/ounce and protein for fortified human milk (HM) only.
[c]Increasing enteral volume to ≥180 mL/kg with fortified HM may provide excessive nutrient intake.
HMF, human milk fortifier; PF, premature formula; TPN, total parenteral nutrition.