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Original Article

Early provision of oropharyngeal colostrum leads to sustained breast milk feedings in preterm infants

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Background: Oropharyngeal colostrum (OC) application strategies have been shown to be feasible and safe for very low birth weight (VLBW) infants. Evidence to support the nutritional and clinical advantages of OC care remains somewhat theoretical. The objectives of this study were to a) confirm the feasibility and safety of OC application in preterm infants and b) determine if OC application is associated with improved nutritional and clinical outcomes from birth to discharge. We hypothesized that OC application in the first few days would promote sustained breast milk feedings through discharge.
Methods: An observational longitudinal study was conducted in 133 VLBW infants during 2013–14, after an OC protocol was adopted. Maternal and infant characteristics, infant vital signs during administration, nutritional outcomes, and common neonatal morbidities were assessed and compared to 85 age- and weight-matched VLBW infants from a retrospective control cohort from 2012, prior to the implementation of the OC protocol.
Results: There were no adverse events or changes in vital signs during the application of OC. VLBW infants who received OC continued to receive the majority of their enteral feeds from human breast milk at six 6 of age and through discharge ($p < 0.01$). There was no difference in maternal characteristics known to affect breast milk production, and rates of common neonatal morbidities were statistically similar between groups.

Abbreviations: BPD, bronchopulmonary dysplasia; DOL, day of life; BM, breast milk; BPD, bronchopulmonary dysplasia; IVH, interventricular hemorrhage; NEC, necrotizing enterocolitis; NPO, nil per os; NICU, neonatal intensive care until; OC, oropharyngeal colostrum; PICC, peripherally inserted central catheter; ROP, retinopathy of prematurity; SIP, spontaneous perforations; TPN, total parenteral nutrition; VAP, ventilator associated pneumonia; VLBW, very low birth weight.

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Conclusion: OC application for VLBW infants is safe and practical in a neonatal intensive care unit setting and is associated with increased rates of breast milk feeding.

1. Introduction

Human breast milk is the best source of nutrition for newborn babies, prompting recommendations that infants be exclusively breastfed for the first six months of life.[1] In addition to the nutritional benefits of breast milk, it also contains important digestive enzymes, immunological and anti-inflammatory factors, antioxidants, growth factors and hormones that all contribute to improved neonatal host immune defense and overall long-term health.[2–4] Breastfed infants are often less susceptible to infection and metabolic disorders (i.e., obesity and/or type II diabetes), and may have improved neurodevelopmental and cardiovascular outcomes in later life.[5–9] Nonetheless, breastfeeding rates remain suboptimal, most notably among premature infants, who may most greatly benefit from the protective effects of human breast milk.[10,11] Sustained breast milk feedings has been shown to decrease the incidence and severity of several common neonatal complications of prematurity, such as necrotizing enterocolitis (NEC), sepsis, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), feeding intolerance and neurodevelopmental impairment.[12–15] Despite the many advantages associated with providing maternal breast milk d to premature infants, several barriers remain that disrupt the relationship and often overshadow the opportunities to promote and provide human breast milk feedings.[16]

In the immediate postnatal period for very low birth weight (VLWB) infants, enteral feedings are not always possible and oral feedings are not practical because of developmental immaturity.[17] To bridge the gap to the introduction of enteral breast milk, the practice of early application of oropharyngeal colostrum (OC) was proposed as a protective strategy.[18] This application of OC in this early neonatal period is feasible and safe for VLBW infants that are not yet able to receive enteral feeds.[18–24] Immunoprotective factors are more highly concentrated in the colostrum of mothers who deliver preterm infants and may offer many of the same protective and immunological benefits as those observed from human breast milk.[21–28] However, there is limited evidence to support the biological and clinical advantages of OC care.[21,22] We hypothesized that the benefits of OC are not limited to the direct protection against serious clinical outcomes, but in fact, mothers who provide OC to VLBW infants in the first few days will continue to provide breast milk for a longer period of time. Therefore, we performed an observational longitudinal study in VLBW infants to confirm the feasibility of OC application in VLBW infants, and determine the short- and long-term effect of OC by evaluating its impact on nutritional and clinical outcomes.

2. Methods

2.1. Study population

We prospectively monitored and longitudinally followed 133 VLBW infants (<1500 g) from birth through discharge in the neonatal intensive care unit at Goryeb Children's Hospital, Morristown, NJ, between January 2013 and December 2014. In January 2013, an OC protocol was adopted for VLBW infants whose mothers provided their own colostrum.[18–20,29] (Appendix). A separate retrospective control cohort of VLBW infants from 2012 (n = 85), immediately prior to initiation of the OC protocol (pre-OC), was included in the study and compared to the infants in the OC protocol. Maternal support and education on the benefits of using breast milk did not change over the course of the study and was the same for both the OC and pre-OC cohorts. The OC protocol was not part of a new feeding protocol. In our unit, a feeding protocol for VLBW infants was established in 2010, and therefore was the same for both the cohort enrolled in the OC protocol and the pre-OC cohort in this study. Infants with suspected congenital anomalies, congenital heart disease (except hemodynamically insignificant ventricular or atrial septal defects), congenital gastrointestinal or renal anomalies, or history of maternal substance abuse were excluded from the study. The same exclusion criteria applied for the experimental and control groups. Infants that did not receive OC because of maternal illness or unavailability of mother's first milk were also excluded. The institutional review board at Atlantic Health System approved the study. Written informed consent was obtained from the parents or guardians of all participants.

2.2. Oropharyngeal colostrum (OC) protocol

The OC protocol was stratified by birth weight, so that infants weighing less than 1000 g (n = 51) received 0.1 ml of colostrum via syringe or swab to each buccal mucosa (0.05 ml/side), and infants weighing between 1000 and 1500 g (n = 82) received 0.2 ml colostrum to each buccal mucosa (0.1 ml/side), every 2–4 h in addition to standard patient care for five days, (anticipated number of doses ranged from 30 to 60). Vital signs were monitored during OC application, and the procedure was immediately stopped if the infant had a desaturation episode with oxygen saturation less than 85%, bradycardia (heart rate, HR < 100/min), tachycardia (HR > 200/min), tachypnea (respiratory rate, RR > 80/min), or apnea. The mothers were given verbal education on the proposed benefits of providing OC to their infants. Maternal characteristics that

influence the production of breast milk were documented at the time of delivery (Table 1) and infant demographics were recorded upon neonatal intensive care unit (NICU) admission (Table 2).

2.3. Data collection

The following nutritional outcome measures were assessed; time of first OC dose (hours), total number of doses, day of life (DOL) first feeds, DOL infants regained birth weight, DOL infants reached 120 ml/kg/day feeds, type of first feeds (breast milk or preterm formula), and the majority of feeds (>50% breast milk, unfortified or fortified; formula only; or a combination of breast milk and formula) at 1 week of age, 6 weeks of age, and at discharge. The morbidities monitored were central line days, NEC (medical and surgical, ≥Bells stage 2), spontaneous intestinal perforation (SIP, pneumoperitoneum with pneumatosis from a single intestinal perforation), suspected sepsis, ventilator associated pneumonia (VAP, culture positive tracheal aspirate specimen), ROP (stage 2 or higher), bronchopulmonary dysplasia (BPD, National Institutes of Health [NIH] workshop definition), interventricular hemorrhage (IVH Grade III/IV), and death.

2.4. Statistical analysis

All data are expressed as median values (interquartile ranges) or percentages. Continuous variables were tested for normality using the Kolmogorov–Smirnov test and a histogram illustration of the data. Comparisons were adjusted for gestational age at birth. Unpaired *t*-test or Mann Whitney *U* test, where appropriate, was used to compare the two groups: (a) pre-OC protocol (n = 85); and OC protocol (n = 133). We controlled for the maternal characteristics and infant characteristics (Tables 1 and 2) in the analysis. All of the maternal and infant characteristics, as well as the infant nutritional and clinical outcomes, were collected by one observer (A.H.) blinded to the clinical status of the VLBW infants. We assigned $p < 0.05$ as statistically significant (Stata 13.0; StataCorp, College Station, TX).

Table 1 Maternal characteristics for pre-oropharyngeal (OC) and OC protocol cohorts.

	Pre-OC protocol (n = 85)	OC-protocol (n = 133)	*p*-Value
Age (years)	33 (29,35)	32 (28,35)	0.82
BMI (kg/m^2)	29 (26,34)	29 (26,34)	0.68
Gravida	2 (1,3)	2 (1,3)	0.12
Chorioamnionitis (yes)	1 (1%)	4 (3%)	0.40
Pre-eclampsia	16 (19%)	20 (15%)	0.60
Premature rupture of membranes	4 (5%)	10 (8%)	0.45
Smoking (yes)	4 (5%)	10 (8%)	0.45
Alcohol (yes)	0	0	NA
Mode of delivery (C-section)	73 (86%)	106 (80%)	0.06
Maternal illness			
Gestational hypertension	6 (7%)	8 (6%)	0.45
Gestational diabetes mellitus	5 (6%)	7 (5%)	0.65
Maternal hypothyroidism	5 (6%)	8 (6%)	0.42

Data are presented as median values.

Table 2 Infant characteristics.

	Pre-OC protocol (n = 85)	OC-protocol (n = 133)	*p*-Value
Gestational age (weeks)	28 (26,30)	28 (26,30)	0.69
Birth weight (grams)	1060 (817,1345)	1025 (805,1275)	0.50
Birth weight strata, n (%)			
500–749	16 (19%)	27 (20%)	0.45
750–999	20 (24%)	38 (29%)	0.56
1000–1249	22 (26%)	32 (24%)	0.73
1249–1500	27 (31%)	36 (27%)	0.42
Gender (female)	47 (55%)	61 (46%)	0.12
Race			0.78
Caucasian	55 (65%)	93 (70%)	
Black	11 (13%)	10 (8%)	
Asian	13 (15%)	19 (14%)	
Other	6 (7%)	19 (14%)	

Data are presented as median (interquartile ranges) or number (percentage).
NA, not applicable.

3. Results

There were 96 VLBW infants admitted to our NICU in 2012, of which 85 infants (89%) met eligibility criteria for this study. After the initiation of our OC protocol, there were 189 VLBW infants admitted to our NICU (2013–2014), of which 156 infants (83%) were eligible to receive OC. Thirty-three of these eligible infants did not receive OC due to maternal illness or decision, or inability to provide breast milk. Therefore, 218 infants were included in this study, 85 in the pre-OC protocol and 133 in the OC-protocol (Fig. 1). Among infants that received OC, the median time for OC initiation was 24 h after birth (interquartile range [IQR]: 12 to 43), and these infants received a median number of 27 OC doses (IQR: 20 to 33). There were no adverse changes in vital signs during the application of OC in any of the infants. Specifically, there were no episodes of hypotension, apnea, bradycardia, or desaturations associated with the application of OC. Maternal characteristics were similar between the OC and non-OC groups (Table 1). Infant demographics are summarized in Table 2.

In our study, the day of life (DOL) that feeds were initiated, DOL infants regained their birth weight, and the DOL they reached 120 ml/kg/day feeds were unchanged between

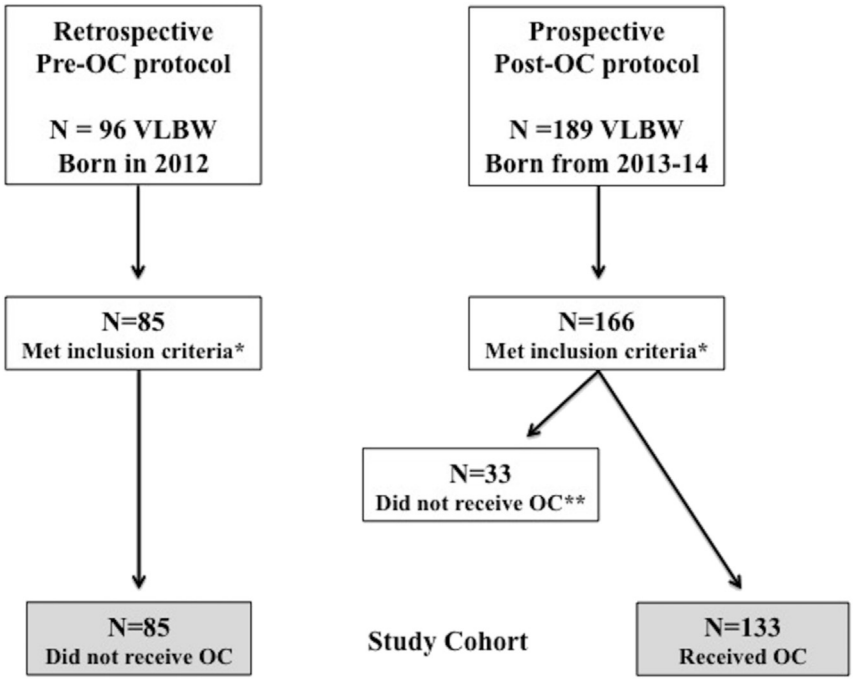

Fig. 1 Study Subject Flow Diagram: * Infants with suspected congenital anomalies of the airway, congenital heart disease (except hemodynamically insignificant ventricular or atrial septal defects), congenital gastrointestinal or renal anomalies, or history of maternal substance abuse were excluded from the study. ** For 33 out of the 166 eligible infants that did not receive OC, we noted that maternal illness, or maternal unwillingness prevented colostrum from being collected.

the groups, irrespective of gestational age at birth. There was no difference in the DOL for first feeds or majority type of feeds during the first week of life. However, there was a significant association between OC application and receiving breast milk as the majority of enteral feeds at 6 weeks of age ($p = 0.03$) and through discharge ($p = 0.007$). These outcomes remained consistent when adjusted for maternal characteristics known to affect breast milk production, gestational age at birth, time to OC initiation, and total number of doses (Table 3). There were no statistical improvements in the incidence of common neonatal morbidities among infants that received OC care. The occurrence of NEC, SIP, sepsis, VAP, ROP, IVH, or BPD was all statistically similar between groups (Table 4).

4. Discussion

To our knowledge, this is one of the largest evaluations on the impact of early OC application on clinical and nutritional outcomes in VLBW infants from birth through discharge. Our study results are in-line with a growing collection of evidence that suggests OC care is safe and feasible in VLBW infants.[18–20] In this study we also considered maternal characteristics that may affect breast milk production: most notably, we were able to show that the initiation of an OC protocol at our center is associated with the increased rate of breast milk feeding through discharge.

4.1. Feasibility and safety

The safety of OC for VLBW infants has been broadly explored by Rodriguez et al.[18] and others.[18–20,22,27,30] While the strategies for OC care among these studies have differed slightly, they have consistently shown that the application of OC does not lead to adverse clinical events (agitation, aspiration, bradycardia, or tachycardia) or disrupt standard of care. Similarly, the VLBW infants that received OC in our study did so without incident (of these 65 were extremely low birth weight). We found that mothers were generally willing to provide colostrum for OC application, which allowed 81% of eligible VLBW infants to receive OC.

In more recent studies, the feasibility of OC application for critically ill VLBW infants has been explored; specifically by assessing the use of OC in ventilated VLBW infants, and by attempting to administer OC at earlier times and for more sustained periods.[20] In previous studies, most found it impractical to administer colostrum during the first 24 h after birth, and on average, neonates were older than 2 days upon initiation of OC.[18–20,22,27,29,30] In our study, we also made every attempt to initiate OC as early as possible and found that the median time for OC initiation was 24 h after birth (IQR: 12 to 43). Despite this success, the variability we experienced in OC initiation, and instances of late OC initiation, nearly always correlated to the time milk expression was initiated in new mothers. At our center, we estimate that the average time to start milk expression in mothers of NICU infants is about 6–8 h after delivery; a timeframe that generally allows for OC application within the first 24 h after birth.

Additional determinants of OC feasibility are the percentage of planned doses administered and frequency. In separate studies, Montgomery et al. and Lee et al. found that 75–80% of the planned swabbings were actually given

Table 3 Nutritional outcomes.

	Pre-OC protocol (n = 85)	OC protocol (n = 133)	*p*-Value
First OC dose (hours)	NA	24 (12,43)	
Number of OC doses	NA	27 (20,33)	
Day feeding began	2 (1,3)	1 (1,2)	0.22
Day regained birth weight	10 (8,13)	9 (7,12)	0.85
Day reach 120 ml/kg/day	12 (9,19)	15 (12,23)	0.29
First feeding?			0.56
Breast milk	50 (59%)	73 (55%)	
Formula	35 (41%)	60 (45%)	
First week feeding (majority)			0.54
Breast milk	70 (83%)	120 (90%)	
Formula	13 (15%)	7 (5%)	
NPO	2 (2%)	6 (4%)	
Six week feeding (majority)[a]			0.03
Breast milk	47 (55%)	89 (67%)	
Formula	26 (31%)	24 (18%)	
Discharge feeding[b]			0.007
Breast milk	27 (32%)	70 (53%)	
Formula	46 (54%)	47 (35%)	
Mixture	10 (12%)	9 (7%)	

Data are presented as median (interquartile ranges) or number (percentage); NA, not applicable.

[a] At six weeks, 12 (14%) and 20 (15%) were already discharged from the pre-OC and OC protocol groups, respectively. At six weeks of age, infants received either fortified breast milk or formula.

[b] At discharge, infants received unfortified breast milk, fortified breast milk, formula, or a mixture of formula and breast milk.

Table 4 Clinical outcomes.

	Pre-OC protocol (n = 85)	OC-protocol (n = 133)	*p* Value
PICC line days	11 (7,19)	10 (6,19)	0.30
Medical NEC	6 (7%)	9 (7%)	0.88
Abdominal surgery			
SIP	5 (6%)	4 (3%)	0.27
Surgical NEC	4 (5%)	6 (5%)	0.85
Suspected sepsis	3 (4%)	10 (8%)	0.32
VAP (yes)	0	3 (2%)	0.19
ROP (stage 2 or higher)	11 (13%)	12 (9%)	0.51
IVH (Grade III or IV)	4 (5%)	7 (5%)	0.66
BPD	18 (21%)	20 (15%)	0.41

Data are presented as median (interquartile ranges) or number (percentage).
PICC, peripherally inserted central catheter.
SIP, spontaneous intestinal perforation.
NEC, necrotizing enterocolitis (≥Bell's stage 2).
VAP, ventilator associated pneumonia.
ROP, retinopathy of prematurity.
IVH, intraventricular hemorrhage.
BPD, bronchopulmonary dysplasia.

as proposed every 3 h.[27,30] In an ongoing randomized control trial to determine the efficacy of OC for VLBW infants, completed treatment is defined as having received at least 70% of planned doses.[31] In our study, the median number of doses was 27 (IQR: 20 to 33). Although this falls short of our goal for OC application every 2 h for 5 days (goal: 60 doses), it is >70% of planned doses for OC application every 4 h for 5 days (goal of 30 doses). Overall, this reflects a strategy of minimal stimulation employed by the nurses, who preferred not to handle the infants more than every 3–4 h while simultaneously checking vitals.[32] Additionally, planned OC doses may have been missed if fresh or refrigerated colostrum was not available, if OC application was discontinued at the time enteral feeds were started, or based on the acuity of NICU infants and staffing demands. In our analysis, infants who received OC were still more likely to be discharged home on breast milk, irrespective of the total number of received doses in the first 5 days of life.

4.2. Nutritional outcomes

Recently, investigators have described improvements to several nutritional outcomes for VLBW infants because of OC application or a standardized feeding protocol that includes OC care.[19,29] 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.[19] Additional studies suggest that OC application may also reduce the amount of time an infant requires total parenteral nutrition (TPN) and decrease the number of peripherally inserted central catheter (PICC)-line days.[29] Unlike these previous studies, we found no difference in the time to initiate enteral feeds or the time to reach full feeds between infants that did and did not receive OC. In part, our result likely reflects the recent change in NICU culture to start trophic feeds as early as possible.[33] In a recent study, Romano-Keeler et al.[17] also observed no difference in the time to initiate enteral feeds (median age of 2 days) between groups, further validating this cultural shift. Similar to Lee et al.[27] we also found no difference in the time it took for infants to regain their birth weight and no difference in time to reach full enteral feeds.

In this study, there was no association between OC application and the first feed or majority of enteral feeds in the first week of life. These results may be explained by the fact that maternal support and education on the benefits of breast feeding, timely lactation, and milk expression were consistent throughout the study period for both the pre-OC and OC cohorts, and the feeding protocol did not change upon the implementation of an OC protocol. On the other hand, there was an association between OC application and receiving breast milk as the majority of enteral feeds at 6 weeks of age, and through discharge. While the biological explanation of this association is unclear, we hypothesize

that even with the same maternal education and support for the two cohorts, OC application may have provided an additional psychological boost to mothers by allowing them to participate in their infant's first oral experience. We speculate that in this way, OC care can strengthen the mother—infant dyad interaction, even at a time of minimal handling and stimulation, which can lead to positive long-term nutritional benefits.

In our center, infants <1500 g receive bovine fortifiers when they reach 100 ml/kg/day feeds and they remain on fortification through discharge. We did not assess whether OC care and/or fortification alters important metabolic factors, such as the level of alkaline phosphatase. We also did not consider the use of donor human milk as a source of OC; future work is needed to explore its role and benefits in this capacity. Despite these limitations, our preliminary observations on the nutritional benefits of OC are important to the field.

4.3. Secondary outcome measures

Theoretical evidence suggests that colostrum may be an ideal "first immune stimulator" for premature infants[21,22]; and indeed premature human colostrum has higher concentrations of proteins, cytokines, and secretory immunoglobins compared with term colostrum or mature milk.[26,27,34] Several authors have recently described the theoretical mechanisms by which the immunologic factors in OC may stimulate and protect the immature neonatal immune system. Recently, a set of small published studies have shown that OC application may lead to a reduction in clinical morbidities in VLBW infants, such as NEC, sepsis, VAP, and SIP,[12,19,29,35] whereas other studies have been inconclusive with respect to some of these clinical outcomes.[19,27] Although we did not find a reduction in the incidence of common neonatal morbidities in these infants in this study, it was underpowered to detect significant differences in most of the common morbidities of prematurity because of the lack of robust literature linking them to OC care. This limitation restricts our ability to make conclusive statements about whether OC application alters a premature infant's risk for these morbidities.

4.4. Limitations of this study

This study involved a comparison of two cohorts of VLBW infants, one studied before and one studied after implementation of a clinical protocol for OC application in the NICU. Such nonconcurrent comparisons did not allow for evaluation of cytokine, chemokine, and antioxidant defense system profiles in both periods, thus limiting our ability to retrieve information regarding these factors. An adequately powered, randomized controlled trial to evaluate the influence of OC administration on these common clinical outcomes and immunological markers is needed to provide more robust evidence for the efficacy of OC.[27,31]

5. Conclusion

In this study, we confirmed that OC application is safe and practical in VLBW infants and found that implementation of an OC protocol is associated with increased breast feeding rates at 6 weeks, and through discharge. Given the undeniable benefits of breast milk for VLBW infants, OC may serve as a catalyst for increasing breastfeeding rates and duration among premature infants.

Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

Compliance with ethical standards

This study was not externally funded. All procedures performed in this study followed ethical standards.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pedneo.2017.04.003.