


Short-Term Outcomes of Early Oral Colostrum Administration in VLBW Neonates: An Open-Label Randomized Controlled Trial

Sedigheh Tehranchi¹, Farzaneh Palizban^{1*} , Maryam Khoshnood Shariati¹, Naeeme Taslimi Taleghani¹, Arefeh Fayazi², Mohammad Farjami³

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Abstract

Background: Oropharyngeal colostrum priming (OCP) has been proposed as a potential nutritional option for very low birth weight (VLBW) newborns. This study aimed to determine short-term outcomes of early oral colostrum administration in VLBW neonates.

Methods: This open-label randomized controlled trial was conducted on VLBW neonates admitted to Mahdiah Hospital, Tehran, Iran, between February and December 2022. According to the protocol, all eligible neonates were randomized evenly to the intervention group, which received oral colostrum (OC), and the control group, which received no OC. Finally, short-term outcomes of early OC administration were compared between groups using the independent-samples t test, chi-square, and Fisher exact tests.

Results: Of 80 randomized neonates, 37 and 39 from the intervention and control groups entered the final analysis, respectively. Neonates in the intervention and control groups did not significantly differ in terms of peripherally inserted central catheter (PICC) infection ($P = 0.728$), sepsis ($P = 0.904$), necrotizing enterocolitis (NEC) ($P > 0.999$), intraventricular hemorrhage (IVH) ($P = 0.141$), retinopathy of prematurity (ROP) ($P = 0.923$), and bronchopulmonary dysplasia (BPD) ($P = 0.633$). Furthermore, there was no significant difference between groups considering the time to reach 120 cc/kg feeds ($P = 0.557$), time to reach birth weight ($P = 0.157$), length of hospitalization ($P = 0.532$), and mortality rate ($P = 0.628$).

Conclusion: The results of our study revealed that despite safety, early OC administration did not improve any of the short-term outcomes in VLBW neonates.

Keywords: Colostrum, Very Low Birth Weight, Neonate, Breast Milk

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Introduction

Human breast milk is the optimal container for all neonatal nutritional and immunological requirements. The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for the first 6 months of life and continued

breastfeeding for a year or more, which is assented to by the World Health Organization (WHO) (1, 2), Center for Disease Control and Prevention (CDC), and almost all other medical societies (3). On the other hand, preterm birth

Corresponding author: Dr Farzaneh Palizban, palizbanfarzaneh@sbmu.ac.ir

¹ Clinical Research Development Center, Mahdiah Educational Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

² Family Health Research Institute, Maternal-Fetal and Neonatal Research Center, Tehran University of Medical Sciences, Tehran, Iran

³ Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

↑What is “already known” in this topic:

Oropharyngeal colostrum priming (OCP) has been proposed as a potential nutritional option for very low birth weight (VLBW) newborns. Results showed that breast milk administration decreases early morbidities (sepsis, necrotizing enterocolitis, and milk intolerance) in preterm infants. Despite all the theoretical advantages of OCP, limited clinical evidence supports the benefits of oral colostrum (OC) care in VLBW infants.

→What this article adds:

We compared the administration of OC versus no OC in VLBW infants and found that despite safety, early oral colostrum administration did not improve any of the short-term outcomes in VLBW neonates.

is an intricate health problem and a multifactorial situation. Previous studies demonstrated that 29% of neonatal mortalities and morbidities are related to preterm birth complications (4, 5).

Oropharyngeal colostrum priming (OCP) has been proposed as a potential nutritional option for very low birth weight (VLBW) newborns (6). In addition to nutrients, human breast milk contains several bioactive factors, such as different cells, anti-infectious and anti-inflammatory agents, tissue growth factors, and prebiotics, which meet all neonatal needs at different stages of growth (7). According to the literature, breast milk administration decreases early morbidities (sepsis, peripherally inserted central catheter [NEC], and milk intolerance) and late morbidities (obesity, diabetes, and cardiovascular diseases) in preterm infants, as well as subsequent mortalities in them (8-13).

Oral feeding with breast milk is not always practical in preterm infants due to maturity issues or other complications secondary to the gestational age. Most preterm infants require respiratory support, thereby rendering feeding more challenging (14). The early oral administration of colostrum (OCP) can affect microbial colonization in neonates (15). Furthermore, OCP decreases the incidence of sepsis and increases circulating levels of immune components, especially in extremely preterm infants (<28 weeks) (16, 17). Several studies have demonstrated that the early administration of OC in preterm infants is somewhat safe and uncomplicated, particularly in VLBW infants (18-20). A clinical trial conducted in Spain has revealed that OCP administration did not affect outcomes like NEC and sepsis (21). Also, a meta-analysis of randomized control trials demonstrated that OCP can reduce the incidence of NEC among premature infants. Meanwhile, the incidence of intraventricular hemorrhage (IVH) and retinopathy of prematurity (ROP) did not differ between intervention and control groups (22).

Despite all the theoretical advantages of OCP, limited clinical evidence supports the benefits of OC care in VLBW infants (23). Thus, this study aimed to determine short-term outcomes of early OC administration in VLBW neonates.

Methods

Study Design and Setting

The protocol for this open-label randomized controlled trial was registered to the Iranian Registry of Clinical Trials (ID: IRCT20220424054629N1). The study was conducted at Mahdiah Hospital (Tehran, Iran) between February and December 2022. The inclusion criteria were as follows: neonates weighing <1500 grams who were admitted to the neonatal intensive care unit (NICU), and the possibility of initiating the OC protocol within the first 96 hours of life. Also, neonates with the following features were excluded from the study: congenital anomaly syndromes, congenital gastrointestinal anomalies, maternal HIV infection, maternal drug abuse, neonatal asphyxia, underlying diseases in mothers, and unavailability of breast milk.

Sampling, Randomization, and Blinding

In this study, data were collected based on consecutive

sampling. Based on a study by Ferreira et al (24) and considering μ_1 (time to reach 120 ml/kg/day feeds) = 24, μ_2 = 20, δ_1 = 7, δ_2 = 8, α = 5%, and power = 75% the sample size was estimated to be 43 patients for each group. Samples were allocated to the intervention and control groups using the block random method. The RAS statistical software was utilized to determine the sequence of the blocks. The capacity of the blocks considered 4 samples with the following permutations for each block: (ABAB), (AABB), (BBAA), (BABA), (ABBA), and (BAAB). This study was also an open-label controlled trial with no blinding.

Oral Colostrum Protocol

The OC protocol of Mahdiah Hospital was previously validated for VLBW infants (20, 21). In the intervention group, the OC protocol was administered by trained nurses as 0.2 mL/side or 3 drops/side every 3 hours to each buccal mucosa via wearing sterile gloves and using 24-gauge needleless tuberculin syringes, continued to the beginning of oral feeding. Precise vital sign monitoring was done during the administration of the OC. In case of an adverse complication such as a hypoxic episode (blood oxygen saturation <88%), tachypnea (respiratory rate >80/min), apnea, bradycardia (heart rate <100/min), and tachycardia (heart rate >200/min), the process must have been stopped immediately. The neonates in the control group did not receive OC until oral feeding was begun.

Data Collection

All neonates were closely monitored from birth until discharge or death. The baseline characteristic features of the neonates (age, sex, and APGAR scores) were collected by reviewing medical records.

As the primary outcome, the nutritional outcomes of OCP were assessed using DOL (day of life) for the first feeds, time to reach birth weight, and time to reach 120 mL/kg/day feeds. The following variables were considered secondary outcomes of early OCP: PICC, sepsis, NEC, IVH, ROP, bronchopulmonary dysplasia (BPD), length of hospitalization, and mortality.

Statistical Analysis

The data were processed using SPSS software Version 23.0, with the significance level set at 0.05. Variables were described as frequency, percentage, mean, and standard deviation. The chi-square and Fisher's exact tests were used to compare qualitative variables between groups. Furthermore, the independent-samples t test was used to compare quantitative variables between groups.

Ethical Considerations

The ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran, approved the study with the ID number IR.SBMU.RETECH.REC.1399.1271. After providing comprehensive explanations to the parents of the studied neonates, they were asked to sign a written informed consent form.

Results

Out of 80 randomized neonates, they were equally allocated to the intervention and control groups. During the study, 3 and 1 neonates were excluded from the intervention and control groups, respectively. Thus, 76 neonates entered the final analysis. Figure 1 depicts the flow chart of the study.

Table 1 shows the baseline characteristics of the neonates. Neonates in the intervention and control groups did not differ considering age (2.00 ± 2.06 days vs 2.07 ± 2.04 days, $P = 0.803$), birth weight (1282.70 ± 348.82 gm vs 1280.25 ± 293.01 gm, $P = 0.974$), and APGAR scores at 5 minutes (8.45 ± 1.72 vs 8.10 ± 1.69 , $P = 0.284$). The application of OC did not lead to adverse complications presented by hypoxia, apnea, tachycardia, or bradycardia (Table 2).

Table 2 demonstrates the short-term outcomes and safety of OCP in hospitalized neonates. Neonates in the intervention and control groups did not significantly differ in terms of peripherally inserted central catheter (PICC) infection (54.1% vs 57.9% , $P = 0.728$), sepsis (16.2% vs 17.9% , $P =$

0.904), NEC (0% vs 2.6% , $P > 0.999$), IVH (13.5% vs 20.6% , $P = 0.141$), ROP (27% vs 28.2% , $P = 0.923$), and BPD (10.8% vs 17.9% , $P = 0.633$). Moreover, there was no significant difference between groups considering time to reach 120 cc/kg feeds (14.64 ± 6.95 vs 13.17 ± 7.20 , $P = 0.557$) and time to reach birth weight (12.64 ± 4.49 vs 14.62 ± 6.43 , $P = 0.157$). The length of hospitalization in the control group was longer than in the intervention group with no significant difference (31.61 ± 22.49 vs 28.57 ± 19.19 , $P = 0.532$). Also, the mortality rate did not significantly differ between intervention and control groups (16.2% vs 10.3% , $P = 0.628$).

Discussion

Colostrum, a type of breast milk produced within 5 days after delivery, is a rich source of biologically active components, such as transforming growth factor- β (TGF- β), immunoglobulin A (IgA), platelet-activating factor, lactoferrin, and oligosaccharides. These factors have an extremely high concentration up to 20 days after delivery, especially in breast milk obtained from mothers of premature

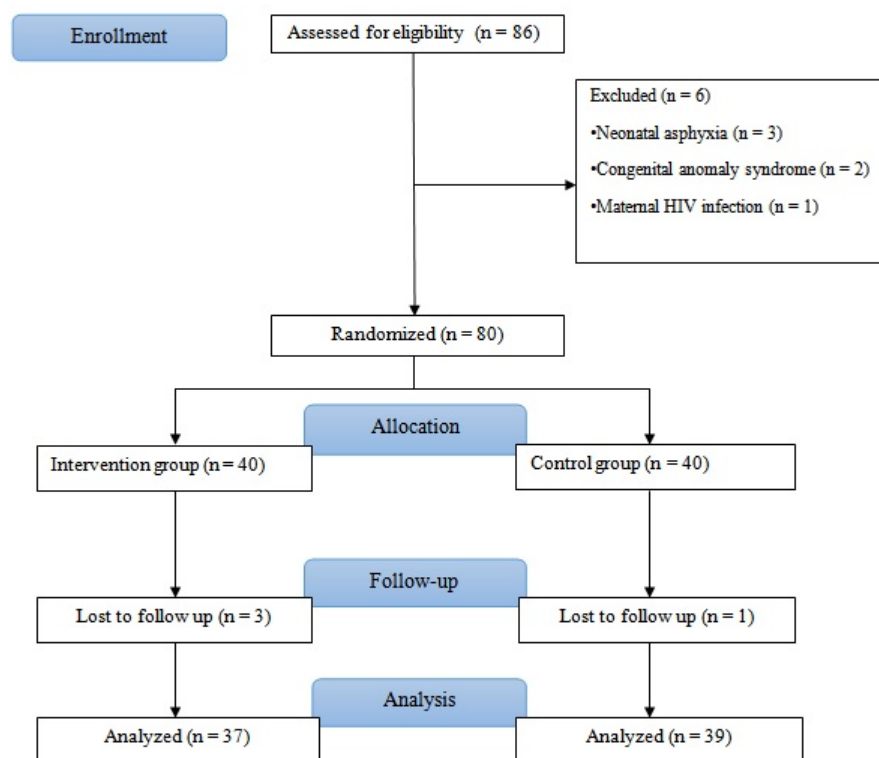


Figure 1. Consort diagram of the study

Table 1. Baseline characteristics of the neonates

Variable	Intervention group (N=37)	Control group (N=39)	Total	P-value
Age at the time of randomization (day)	2.00 ± 2.06	2.07 ± 2.04	2.04 ± 2.05	0.803 ^a
Gender				
Male	16 (43.2)	20 (51.3)	36 (47.4)	0.483 ^b
Female	21 (56.8)	19 (48.7)	40 (52.6)	
Ambiguous	0 (0)	1 (2.6)	1 (1.3)	
Birth weight (g)	1282.70 ± 348.82	1280.25 ± 293.01	1281.10 ± 310.92	0.974 ^a
APGAR score at 1 minute	6.97 ± 2.15	6.51 ± 2.06	6.73 ± 2.09	0.253 ^a
APGAR score at 5 minutes	8.45 ± 1.72	8.10 ± 1.69	8.27 ± 1.70	0.284 ^a

Data were described as frequency (%) or mean \pm standard deviation.

^a independent-samples t-test, ^b Chi-square test

Table 2. Short-term outcomes and safety of OCA in hospitalized neonates

Variable	Intervention group (N=37)	Control group (N=39)	Total	P-value
PICC infection	20 (54.1)	22 (57.9)	42 (56.0)	0.728 ^a
Sepsis	6 (16.2)	7 (17.9)	13 (17.1)	0.904 ^a
Necrotizing enterocolitis	0 (0)	1 (2.6)	1 (1.3)	>0.999 ^b
IVH	5 (13.5)	8 (20.6)	13 (17.1)	0.141 ^b
ROP	10 (27.0)	11 (28.2)	21 (27.6)	0.923 ^a
Bronchopulmonary dysplasia	4 (10.8)	7 (17.9)	11 (14.5)	0.633 ^b
Time to 120cc/kg feeds	14.64±6.95	13.17±7.20	13.88±7.10	0.557 ^c
DOL for feed per gavage	3.41±2.88	3.76±4.78	3.59±3.91	0.938 ^c
DOL for feed per oral	17.73±14.38	19.77±15.56	18.77±15.03	0.777 ^c
Time to reach birth weight	12.64±4.49	14.62±6.43	13.65±5.49	0.157 ^c
Length of hospitalization	28.57±19.19	31.61±22.49	30.13±20.90	0.532 ^c
Death during hospitalization	6 (16.2)	4 (10.3)	10 (13.2)	0.628 ^b
Safety based on adverse complications				
Hypoxia	0 (0)	0 (0)	0 (0)	-
Apnea	0 (0)	0 (0)	0 (0)	-
Bradycardia	0 (0)	0 (0)	0 (0)	-
Tachycardia	0 (0)	0 (0)	0 (0)	-

Data were described as frequency (%) or mean±standard deviation.

Abbreviations, DOL: day of life, IVH: intraventricular hemorrhage, OCA: oral colostrum administration, PICC: peripherally inserted central catheter, ROP: retinopathy of prematurity.

*At the end of the study, 6 and 4 infants from the intervention and control groups had expired, respectively.

^a Chi-square test, ^b Fisher's exact test, ^c independent-samples t-test

neonates. These factors can promote immunocompetence by affecting cells within the oropharyngeal-associated lymphoid tissue and the gut-associated lymphoid tissue and interfere with bacterial colonization (25).

Growth factors and IgA protect against the development of NEC by regulating gut barrier integrity and interfering with microbial colonization. NEC is a life-threatening gastrointestinal disease in newborns, mainly manifested by abdominal distension, vomiting, and bloody stool (26, 27). Based on a study by Mengyue Huo et al, OCP decreased the incidence of NEC, late-onset sepsis (LOS), and severe IVH in preterm infants with a gestational age of <32 weeks. In addition, this study showed that mortality did not differ significantly between neonates under the OCP protocol and the control group. This meta-analysis included 11 randomized controlled trials—with a larger sample size than our study—most of which focused on preterm infants, and not only VLBW infants. NEC and LOS are multifactorial diseases and may be influenced by a variety of variables, including the gestational age, birth weight, and the medical condition of the preterm neonate (27). On the other hand, a study by Aggarwal et al reported that OC administration in very preterm and extremely preterm neonates did not decrease death, LOS, and NEC (28).

We found that OCP could not improve nutritional outcomes in VLBW neonates, which is consistent with some previous studies (16, 29). In contrast, some previous studies provided evidence that OC administration could improve nutritional outcomes for VLBW neonates; for instance, earlier breastfeeding and a shorter time to reach the birth weight and full feeds (1, 17, 30). Furthermore, a recent study by Maraboli Aguilera et al demonstrated that early colostrum administration in VLBW infants was associated

with a greater volume of breastfeeding at discharge (31). These discrepancies may be attributed to different methodologies and sample sizes in previous studies.

Recent studies have provided evidence for the benefits of colostrum priming. The approach to administering oral colostrum in premature and VLBW neonates is more cautious than in term neonates with normal weight. Due to the undeveloped neurogastrointestinal coordination in premature and VLBW neonates, OCP may be accompanied by adverse outcomes, such as aspiration, hypoxia, apnea, bradycardia, or tachycardia (29, 32, 33). In our study, no one showed adverse complications after OCP, which is consistent with the literature, supporting the safety of OCP (34-37).

This study had several limitations. The study was conducted with a small sample size with lower power than usual. Since all neonates were hospitalized and available, we predicted that the dropout rate would be zero, so it was not considered in the calculation of the sample size. However, in practice, a few samples were dropped. Even though every member of the medical team was trained in the OCP protocol, every infant in the trial did not have a private nurse, which may have biased the study's implementation. Moreover, according to the sample size calculation, 43 neonates should remain after randomization. However, 40 neonates were randomized in each group in our study. Furthermore, to protect the safety of neonates in the control group, they did not receive a placebo. A double-blinded study with a placebo control group receiving a placebo can provide more valid results. Thus, it is recommended to perform further studies with a larger sample size and a well-designed methodology to expand our knowledge on this topic.

Conclusion

The results of our study revealed that despite safety, early oral colostrum administration did not improve any of the short-term outcomes in VLBW neonates.

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Ethical Approval

The ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran, approved the study with the ID number IR.SBMU.RETECH.REC.1399.1271. After providing comprehensive explanations to the parents of the studied neonates, they signed a written informed consent form.

Authors' Contribution

S.T., conceptualization and study design; F.P., data collection and writing the original draft. M.K.S., study design and critical editing. N.T.T., supervision and data collection. A.F., critical editing. M.F., data analysis. All authors contributed to the interpretation of the results and have read and approved its final version.

Conflict of Interests

The authors declare that they have no competing interests.

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