Original Article
http://mjiri.iums.ac.ir
Medical Journal of the Islamic Republic of Iran (MJIRI)

Med J Islam Repub Iran. 2024 (23 Jan);38.7. https://doi.org/10.47176/mjiri.38.7

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

Sedigheh Tehranchi[1], Farzaneh Palizban[1]*, Maryam Khoshnood Shariati[1], Naeeme Taslimi Taleghani[1], Arefeh Fayazi[2], Mohammad Farjami[3]

Received: 8 Jun 2023 Published: 23 Jan 2024

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 Mahdieh 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

Conflicts of Interest: *None declared*
Funding: *None*

Cite this article as: Tehranchi S, Palizban F, Khoshnood Shariati M, Taslimi Taleghani N, Fayazi A, Farjami M. Short-Term Outcomes of Early Oral Colostrum Administration in VLBW Neonates: An Open-Label Randomized Controlled Trial x. *Med J Islam Repub Iran.* 2024 (23 Jan);38:7. https://doi.org/10.47176/mjiri.38.7

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, Mahdiyeh 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.

[DOI: 10.47176/mjiri.38.7]

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 Mahdieh 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 Ferreia et al (24) and considering μ_1 (time to reach 120 ml/kg/day feeds) = 24, μ_2 = 20, $\delta_1 = 7$, $\delta_2 = 8$, $\alpha = 5\%$, 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 Mahdieh 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.

[DOI: 10.47176/mjiri.38.7]

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

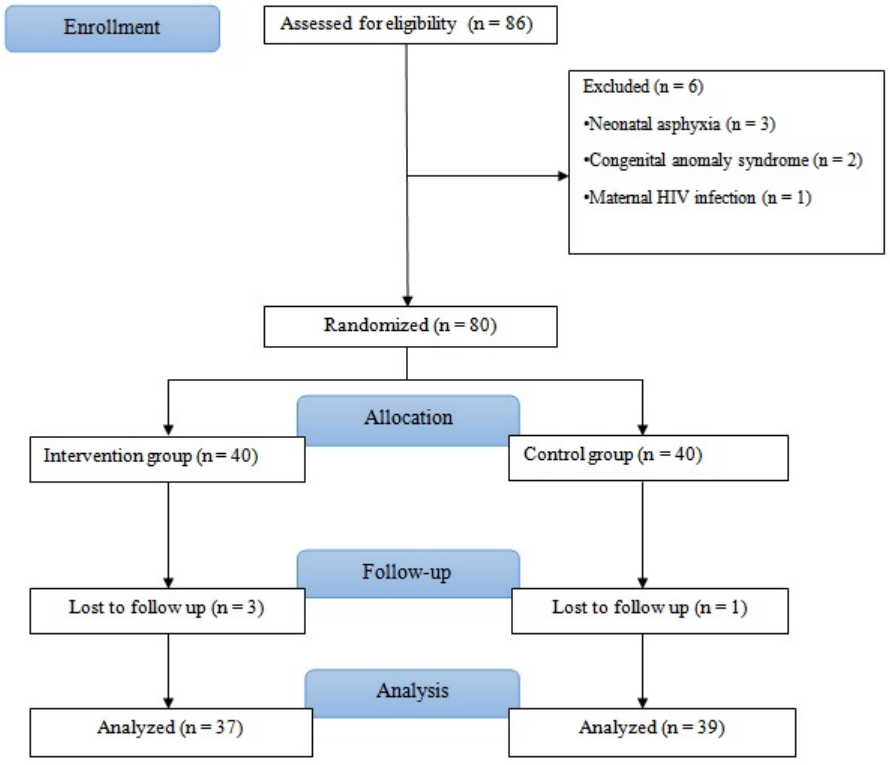

Figure 1. Consort diagram of the study

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±standard deviation.
[a] independent-samples t-test, [b] Chi-square test

[DOI: 10.47176/mjiri.38.7]

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.

[DOI: 10.47176/mjiri.38.7]

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.

Acknowledgments

The authors would like to thank patients and their families.

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.

References

1. Snyder R, Herdt A, Mejias-Cepeda N, Ladino J, Crowley K, Levy P. Early provision of oropharyngeal colostrum leads to sustained breast milk feedings in preterm infants. Pediatr Neonatol. 2017;58(6):534-40.
2. Maastrup R, Hansen BM, Kronborg H, Bojesen SN, Hallum K, Frandsen A, et al. Factors associated with exclusive breastfeeding of preterm infants. Results from a prospective national cohort study. PloS One. 2014;9(2):e89077.
3. RJ S, RJ S. Feeding Strategies for Premature Infants: Beneficial Outcomes of Feeding Fortified Human Milk versus Preterm Formula. J Neonatol. 2000;14(3):42-3.
4. Palizban F, Taslimi Taleghani N, Khoshnood Shariati M, Fallahi M, Tehranchi S, Najafiarab H. Prevalence of Preterm Births and Complications of Prematurity: A Comparison Between First Year of COVID-19 Pandemic and the Previous Year. Arch Pediatr Infect Dis. 2022;10(4):e121163.
5. Buen M, Amaral E, Souza RT, Passini R, Lajos GJ, Tedesco RP, et al. Maternal Work and Spontaneous Preterm Birth: A Multicenter Observational Study in Brazil. Sci Rep. 2020;10(1):9684.
6. Silva AP, Machado RCM, Nascimento BF, da Cunha LVS, Padilha PC. Analysis of clinical outcomes of oropharyngeal colostrum administration in very low-birth-weight preterm newborns. Nutrition. 2021;90:111292.
7. Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. Pediatr Clin. 2013;60(1):49-74.
8. Johnson TJ, Patel AL, Jegier BJ, Engstrom JL, Meier PP. Cost of morbidities in very low birth weight infants. J Pediatr. 2013;162(2):243-9. e1.
9. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA. 2004;292(19):2357-65.
10. Payne NR, Carpenter JH, Badger GJ, Horbar JD, Rogowski J. Marginal increase in cost and excess length of stay associated with nosocomial bloodstream infections in surviving very low birth weight infants. Pediatrics. 2004;114(2):348-55.
11. Patel AL, Johnson TJ, Engstrom JL, Fogg LF, Jegier BJ, Bigger HR, et al. Impact of early human milk on sepsis and health-care costs in very low birth weight infants. J Perinatol. 2013;33(7):514-9.
12. Horta BL, Loret de Mola C, Victora CG. Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: a systematic review and meta-analysis. Acta Paediatr. 2015;104:30-7.
13. Siggers RH, Siggers J, Thymann T, Boye M, Sangild PT. Nutritional modulation of the gut microbiota and immune system in preterm neonates susceptible to necrotizing enterocolitis. J Nutr Biochem. 2011;22(6):511-21.
14. Maron JL, Hwang JS, Pathak S, Ruthazer R, Russell RL, Alterovitz G. Computational gene expression modeling identifies salivary biomarker analysis that predict oral feeding readiness in the newborn. J Pediatr. 2015;166(2):282-8. e5.
15. Sohn K, Kalanetra K, Mills D, Underwood M. Buccal administration of human colostrum: impact on the oral microbiota of premature infants. J Perinatol. 2016;36(2):106-11.
16. Lee J, Kim H-S, Jung YH, Choi KY, Shin SH, Kim E-K, et al. Oropharyngeal colostrum administration in extremely premature infants: an RCT. Pediatrics. 2015;135(2):e357-e66.
17. Seigel JK, Smith PB, Ashley PL, Cotten CM, Herbert CC, King BA, et al. Early administration of oropharyngeal colostrum to extremely low birth weight infants. Breastfeed Med. 2013;8(6):491-5.
18. Rodriguez NA, Meier PP, Groer M, Zeller JM. Oropharyngeal administration of colostrum to extremely low birth weight infants: theoretical perspectives. J Perinatol. 2009;29(1):1-7.
19. Gephart SM, Weller M, Gephart S. Colostrum as oral immune therapy to promote neonatal health. Adv Neonatal Care. 2014;14(1):44-51.
20. Pletsch D, Ulrich C, Angelini M, Fernandes G, Lee D. Mothers'"liquid gold": a quality improvement initiative to support early colostrum delivery via oral immune therapy (OIT) to premature and critically ill newborns. Nurs Leadersh (Tor Ont). 2013;26(34):e42.
21. Martín-Álvarez E, Diaz-Castro J, Peña-Caballero M, Serrano-López L, Moreno-Fernández J, Sánchez-Martínez B, et al. Oropharyngeal colostrum positively modulates the inflammatory response in preterm neonates. Nutrients. 2020;12(2):413.
22. Yan FZ, Huang C, Lei L, Chen LC, Wei LJ, Zhou J, et al. The effect of oropharyngeal colostrum administration on the clinical outcomes of premature infants: A meta-analysis. Int J Nurs Stud. 2023:104527.
23. Rodriguez NA, Caplan MS. Oropharyngeal Administration of Mother's Milk to Prevent Necrotizing Enterocolitis in Extremely Low-Birth-Weight Infants. J Perinat Neonatal Nurs. 2015;29(1):81-90.
24. Ferreira DM, Oliveira AM, de Leves DV, de Bem ÉB, Fatureto GG, Navarro NF, et al. Randomized controlled trial of oropharyngeal colostrum administration in very-low-birth-weight preterm infants. J Pediatr Gastroenterol Nutr. 2019;69(1):126-30.
25. OuYang X, Yang CY, Xiu WL, Hu YH, Mei SS, Lin Q. Oropharyngeal administration of colostrum for preventing necrotizing enterocolitis and late-onset sepsis in preterm infants with gestational age ≤ 32 weeks: a pilot single-center randomized controlled trial. Int Breastfeed J. 2021;16(1):59.
26. Nolan LS, Parks OB, Good M. A Review of the Immunomodulating Components of Maternal Breast Milk and Protection Against Necrotizing Enterocolitis. Nutrients. 2019;12(1).
27. Huo M, Liu C, Mei H, Zhang Y, Liu C, Song D, et al. Intervention Effect of Oropharyngeal Administration of Colostrum in Preterm Infants: A Meta-Analysis. Front Pediatr. 2022;10:895375.
28. Aggarwal R, Plakkal N, Bhat V. Does oropharyngeal administration of colostrum reduce morbidity and mortality in very preterm infants? A randomised parallel-group controlled trial. J Paediatr Child Health. 2021;57(9):1467-72.
29. Romano-Keeler J, Azcarate-Peril MA, Weitkamp J-H, Slaughter JC, McDonald WH, Meng S, et al. Oral colostrum priming shortens hospitalization without changing the immunomicrobial milieu. J Perinatol. 2017;37(1):36-41.
30. McCallie KR, Lee HC, Mayer O, Cohen RS, Hintz SR, Rhine WD. Improved outcomes with a standardized feeding protocol for very low birth weight infants. J Perinatol. 2011;31 Suppl 1:S61-7.
31. Maraboli Aguilera M, Lavanderos Bustamante G, León Martínez C, Zúñiga Ulloa M, Mena Nannig P. [Colostrum protocol evaluation for very low birth weight preterm infants]. Andes Pediatr. 2022;93(3):343-50.
32. Kim JH, Chan CS, Vaucher YE, Stellwagen LM. Challenges in the practice of human milk nutrition in the neonatal intensive care unit. Early Hum Dev. 2013;89:S35-S8.

[DOI: 10.47176/mjiri.38.7]

33. Corpeleijn WE, Vermeulen MJ, Van Den Akker CH, Van Goudoever JB. Feeding very-low-birth-weight infants: our aspirations versus the reality in practice. Ann Nutr Metab. 2011;58(Suppl. 1):20-9.
34. Thibeau S, Boudreaux C. Exploring the use of mothers' own milk as oral care for mechanically ventilated very low-birth-weight preterm infants. Adv Neonatal Care. 2013;13(3):190-7.
35. Nasuf AWA, Ojha S, Dorling J. Oropharyngeal colostrum in preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev. 2018(9).
36. Garofalo NA, Caplan MS. Oropharyngeal mother's milk: state of the science and influence on necrotizing enterocolitis. Clin Perinatol. 2019;46(1):77-88.
37. Ma A, Yang J, Li Y, Zhang X, Kang Y. Oropharyngeal colostrum therapy reduces the incidence of ventilator-associated pneumonia in very low birth weight infants: a systematic review and meta-analysis. Pediatr Res. 2021;89(1):54-62.

[DOI: 10.47176/mjiri.38.7]