Original Article

Oropharyngeal Colostrum Administration in Premature Infants: Impact on Immune Status and Incidence of Common Morbidities

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Abstract

Background: Enteral feeding of preterm infants with maternal colostrum has well-known effects on protecting them, especially against serious infections. This study was conducted to determine whether oropharyngeal administration of colostrum to these infants, soon after birth, has any additional effect on their clinical outcomes and stimulation of their immune system. **Methods:** In this double-blind randomized clinical trial, 60 preterm infants ≤30 weeks' gestation with birth weight ≤1500 g were randomly assigned to receive oropharyngeal colostrum (OAC group) or distilled water (DW group). Primary outcomes were urinary concentration of IgA on days 1, 8, and 15 of birth and incidence of late onset sepsis (LOS) and necrotizing enterocolitis (NEC). Data were analyzed by independent samples *t*-test, repeated measures ANOVA, and Chi-square test using SPSS v. 25. **Results:** The frequency of LOS, NEC, CLD, and mortality and the mean duration of hospitalization and the time to reach full enteral feeding were similar in both groups ($P > 0.05$). The mean of urinary IgA levels increased significantly from the 1st day of birth to the 15th day of birth in the OAC group ($P = 0.013$) but decreased significantly from the 1st day of birth to the 8th and 15th days of birth in the DW group ($P = 0.04$). Results of repeated measures ANOVA test regarding the impact of the two interventions during the studied times on the level of IgA showed that the differences between the means were statistically significant [F (2,116) = 5.12, $P = 0.007$]. **Conclusions:** Oropharyngeal administration of colostrum within the first days of life in preterm infants increases the concentration of IgA in urine. The impact of this immune response on common morbidities of these infants, particularly extremely low gestational age neonates, still needs to be investigated more in other larger studies.

Keywords: *Immune system, oropharyngeal colostrum, preterm infants*

Introduction

Significant advances in perinatal-neonatal medicine in recent decades have led to the survival of a large number of preterm infants, including extremely low birth weight (ELBW) ones. However, increased survival of these infants is associated with significant short- and long-term morbidities such as nosocomial infections, necrotizing enterocolitis (NEC), and permanent neurodevelopmental impairments.

Feeding these infants with breast milk is of particular importance considering its numerous short- and long-term benefits in terms of reducing mortality and common morbidities.[1] The colostrum is rich in cytokines and other immune factors, including lactoferrin and immunoglobulins, which protect the infant against infections with their bacteriostatic, bactericidal, antiviral, anti-inflammatory, and immunomodulatory properties.[2-4] It seems to have a particular role in protecting the premature infants in the first days of life, when they are very sick and exposed to frequent invasive procedures with the highest risk of infection.[2,3] Compared to term infants, the milk of mothers of these infants has less proinflammatory mediators and more anti-inflammatory cytokines. Also, the level of epidermal growth factor in their colostrum is higher. Early administration of colostrum may help balance the inflammatory responses to external stimuli and promote intestinal growth.

The immaturity of the digestive system of premature infants and instability of their clinical condition usually delay enteral feeding and hence receiving colostrum by these infants within the first few days of life. Therefore, it is necessary to consider a safe and effective alternative for

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administering colostrum to this group of infants soon after birth. Oropharyngeal administration of colostrum (OAC) is proposed as a potential option for this purpose.[1-3,5-8] Theoretically, it plays its protective role via several distinctive mechanisms: mucosal absorption of some immune factors, including sIgA (secretory immunoglobulin A) and lactoferrin, interaction of cytokines with cells in the oropharynx-associated lymphoid tissue (OFALT) (as in the case of their interaction with gut- associated lymphoid tissue (GALT) during enteral feeding), and formation of a protective barrier in oral cavity by human milk oligosaccharides (HMOs) against potentially invasive pathogens.[2,3,5] sIgA and lactoferrin may also have such protecting effects by covering the mucosal surface of oropharynx; possibly, some amount enters the upper part of the digestive tract after swallowing and some cover mucosa of the upper respiratory tract.[3,6]

In hospitalized preterm infants who receive human milk via gavage feeding, cytokines, HMOs, sIgA, and lactoferrin do not come into contact with OFALT or the oral mucous membrane of oral cavity. This may be overcome by oropharyngeal administration of colostrum. Hence, OAC should be considered as a supplement to enteral trophic feeding in very premature infants and not as a substitute.[2,3] Despite these theoretical issues about the effects of OAC in very premature infants, there are not many studies in this field, especially randomized clinical trials. Pilot studies conducted on very low birth weight (VLBW) and ELBW infants have shown the feasibility of this method.[3,9] Considering a variety of the outcomes measured and a diversity of the results obtained in these studies, the present study was conducted to determine whether oropharyngeal administration of mother's colostrum to premature infants within the first days after birth has any effect on their clinical outcomes and/or stimulation of their immune system.

Methods

From July 2019 to April 2021, we conducted a double-blind randomized controlled trial in two neonatal intensive care units (NICUs) in Al-Zahra General Hospital and Shahid Beheshti Maternity Hospital, two teaching tertiary hospitals affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. The study protocol was approved by the Ethics Committee of the University; the code was IR.MUI.MED.REC.1398.559. It was registered in Iranian registry of clinical trials (IRCT20171230038142N19). Inborn infants with a gestational age of 30 weeks or less and a birth weight of 1500 g or less were included. Exclusion criteria were history of maternal chorioamnionitis, an Apgar score of 4 or less at 5 min after birth, life-threatening congenital anomalies, evidence of maternal HIV infection (history, pregnancy test), and history of maternal substance abuse. Infants whose mothers could not supply the colostrum in amounts required for the study, those who could not receive trophic feeding during the first 72 hours of birth, those who had early-onset sepsis with positive blood culture or needed to receive aminoglycoside for more than 96 hours after birth, and those who got urinary tract infection[10] were also excluded from the study.

In the study by Lee J *et al*.,[11] urinary levels of sIgA at 1 and 2 weeks after birth were compared in the group who received their mother's colostrum with the group who received sterile water via oropharyngeal route. Based on data of their study, to compare the average urinary concentration of IgA in the two groups with a power of 80% and $\alpha = 0.05$, 60 infants were needed for enrollment.

Interventions

Using block randomization, infants were randomly allocated to one of two groups to receive oropharyngeal colostrum (OAC group) or distilled water (DW group). Informed consent was obtained from the parents before enrolment. Within the first 24 hours after delivery, mothers who participated in the study were educated how to express milk both manually and with electric pumps. Mothers were encouraged to do this every 3 hours and regularly reminded to wash their hands thoroughly before expressing their milk and handling the milk containers.[3,5,11] After providing necessary recommendations, all mothers, regardless of which group the infant is in, were asked to pump their breasts manually as soon as possible. Colostrum were directly expressed into a sterile plastic container. The minimum amount of colostrum considered for a 24-hour period of the study was 3 ml. If this was not provided in one session, the colostrum expressed in subsequent sessions was collected in separate sterile containers up to the required volume. To ensure that colostrum would be supplied for the entire duration of study, every day, the amount needed for one another day was foresight and additionally stored by repeating the above steps once more. A label containing the infant's file number and surname and the date and time of milk expression and colostrum collection was attached on each plastic container, and the containers were placed in the refrigerator at a temperature of 4°C.[3,5,11] Every day, one of the staff of human milk bank who was informed which infant should receive colostrum or distilled water, but not involved in other steps of the study, drew 0.2 ml of colostrum which maximally supplied during the past 24 hours from the container into an insulin syringe without using the needle, and in this way, eight syringes were prepared with colostrum from the same container. If the colostrum of one container was not enough for this purpose, another container from the same time period was used. If the mother was unable to provide the amount of colostrum required for the same 24 hours, the stored colostrum from a day before (as mentioned above) was used[9] To make the content unrecognizable to the nurse who provided care to the infant, each syringe was totally covered with a large white label, on which the date

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and time of preparation and the file number and surname of the infant were written. All eight syringes were placed in a plastic bag labeled with the date and time of preparation and the file number and surname of the infant; the bag was then kept in the refrigerator.[3,5,11]

Similarly, for infants who were allocated to receive distilled water, eight syringes were prepared for a 24-hour period, filled with 0.2 ml of distilled water, and kept in the refrigerator. Every day, the used plastic containers of colostrum were discarded. To blind the study, this was done in the same way for the same number of colostrum containers belonging to the other group. Oropharyngeal administration of colostrum or distilled water was started as soon as possible within the first 36 hours of birth and continued every 3 hours for the following 72 hours.[3,5,11] The nurse who was responsible to administer the content of the syringe was not aware of whether it was colostrum or distilled water. Before the administration, she made sure that there was no secretion inside the infant's mouth and/or nose that required suction. A standard protocol was used for administration: The tip of the syringe was placed on one side of the oral mucosa, pointing back toward the oropharynx, and 0.1 ml of its content was administered for at least 2 minutes. Then, turning it inside the mouth, the remaining 0.1 ml was administered on the other side in the same way.[3,11] During the procedure, monitoring of heart rate, respiratory rate, and capillary oxygen saturation (SpO_2) was continued. In case of bradycardia, tachycardia, tachypnea, apnea, and/or SpO_2 reduction (in amounts that made it necessary to increase FiO_2 by at least 10%), the procedure was immediately stopped and appropriate management took place, wherever it was needed.[3,11] The date and time of each event were recorded, and one additional dose was administered at the end of 72-hour period of the intervention. It was considered to stop the study on the infant if such events were repeated more than 8 times in total. The mouth was not suctioned for at least 1 hour after the procedure, unless needed; in this case, the date and time were recorded and as explained above, one additional dose was administered. A urine sample, including the total volume of urine, was obtained on day 1 of birth before starting the intervention and immediately transferred to the refrigerator at a temperature of 4°C.[10] First, a urine analysis was performed and if there was protein ++ or more (in case of a specific gravity between 1002 and 1015), the sample was discarded and another sample was taken a few hours later. Otherwise, the rest of the sample was centrifuged and frozen at -70°C.[3,11] Similarly, two other samples were taken on days 8 and 15 of birth, repeating the above steps. In each of these 3 days assigned for urine sampling, the presence of protein (as defined earlier) in two specimens taken 12 hours apart led to stopping the study on the infant. The concentration of IgA in urine samples was measured using turbidimetry (Turbosmart: RFID immunoturbidimetry analyzer, TULIP Diagnostics (P) Ltd., Goa, India). Feeding was started as soon as possible, when the infant was clinically stable, in trophic amounts at a rate of 15–20 ml/kg/day; it was gradually progressed after 1–2 days, if tolerated by the infant.

Infants were followed until 36 weeks postmenstrual age or time of discharge from the hospital, whichever came later. The physician who managed the infants during their hospital stay and followed them up was unaware of study group assignment.

Outcomes

Demographic data included infants' gestational age, birth body weight, and gender. Primary outcomes were urinary concentration of IgA on days 1, 8, and 15 of birth and incidence of late onset sepsis (LOS) and NEC. Secondary outcomes included the time to reach full enteral feeding, incidence of chronic lung disease (CLD), defined as oxygen requirement at 36 weeks of postmenstrual age or 28 days after birth, whichever came later, length of hospital stay, incidence of mortality, and adverse events during the intervention (as described above).

Statistical analysis

Data were analyzed using SPSS software for windows version 25 (SPSS Inc., Chicago, IL, USA). Student *t*-test and Chi-square test were used to compare the mean of quantitative [presented as means ± standard deviation (SD)] and qualitative [presented as number (%)] variables, respectively. Analysis of variance (ANOVA) was used for testing the significance levels between the different groups, and ANOVA for repeated measures was used for testing significance levels between the measurement times. Data were analyzed comparing patients in the colostrum group with those in the distilled water group. P value < 0.05 was considered to be statistically significant.

Results

Seventy-four infants were assessed for eligibility. Parents of three infants refused participation of their child in the study, and 11 infants lost to meet all inclusion criteria. A total of 60 newborn infants were allocated to one of the two groups and completed the study [Figure 1].

Baseline characteristics of the studied neonates in the two groups (OAC and DW) are presented in Table 1. There were no significant differences between groups ($P > 0.05$).

Means (SDs) of urinary IgA levels at the 1st, 8th, and 15th days of birth, duration of hospitalization, the time to reach full enteral feeding, and frequency of other studied clinical outcomes in the two groups are presented in Table 2. The frequency of clinical outcomes including LOS, NEC, CLD, and mortality was similar in both groups ($P > 0.05$). The mean duration of hospitalization and the time to reach full enteral feeding were also similar in the two groups ($P > 0.05$). The mean of urinary IgA

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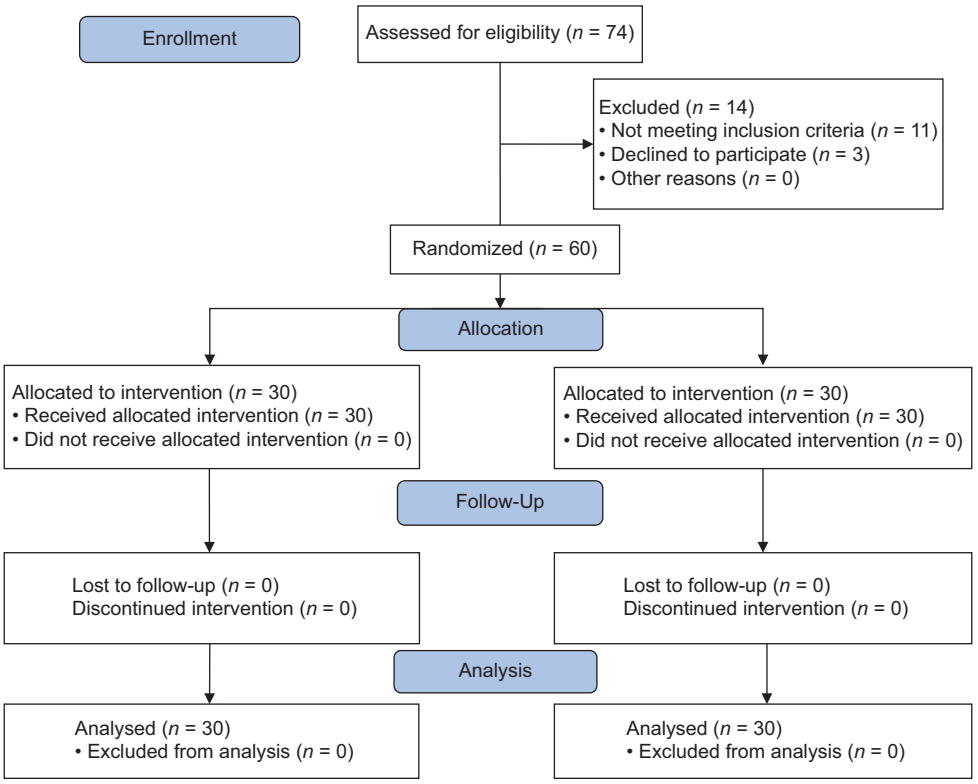

Figure 1: Patients' flow diagram (Consolidated Standards of Reporting Trials, CONSORT)

Table 1: Demographic and baseline characteristics of the preterm infants in the two studied groups

Variable	OAC group *n*=30	DW group *n*=30	*P*
Gender*			0.297
Male	19 (63.3)	15 (50)	
Female	11 (36.7)	15 (50)	
Gestational age (weeks)†	29.3±1.3	29.6±1.3	0.377
Birth body weight (g)†	1249±211	1237±214	0.820

*Data are presented as number (%). †Data are presented as mean±SD. OAC group: received oropharyngeal colostrum, DW group: received oropharyngeal distilled water

levels at the 1st and 8th days of birth were not significantly different between groups (P = 0.795 and P = 0.156, respectively). It was significantly higher in OAC group than DW group at 15th day of life (P = 0.026).

The mean of urinary IgA levels increased significantly from the 1st day of birth to the 15th day of birth in OAC group (P = 0.013). The mean of urinary IgA levels decreased significantly from the 1st day of birth to the 8th and 15th days of birth in DW group (P = 0.04).

Results of repeated measures ANOVA test regarding the impact of the two interventions (administration of oropharyngeal colostrum or distilled water) during the studied times on the urinary level of IgA are shown in Figure 2 [Mauchly's W = 0.72, Mauchly's X^2 test = 18.12, P = 0.000]. The differences between the means were statistically significant [F (2,116) = 5.12, P = 0.007].

The frequency of different adverse events including bradycardia, tachycardia, tachypnea, apnea, and/or SpO2 reduction during administration of all doses of oropharyngeal colostrum or distilled water is presented in Figure 3. There was no significant difference between groups ($P > 0.05$).

Out of 1450 doses, only 52 of such events (3.58%) were observed; in all these cases, the problem was solved immediately after stopping the procedure.

Discussion

The findings of our study showed that the concentration of IgA in urine was significantly increased in very preterm infants who received oropharyngeal colostrum within the first few days of life. Nevertheless, the incidence of common morbidities including LOS, NEC, and CLD and the duration of hospital stay and the time to reach full enteral feeding were not reduced in these infants.

At the time of writing, there have been about 15 articles published regarding the effects of OAC within the first days of life on the clinical outcomes and/or immune status of premature infants. In four of these studies, only clinical outcomes were examined,[4,12-14] of which two articles were randomized clinical trials (RCTs).[12,13]

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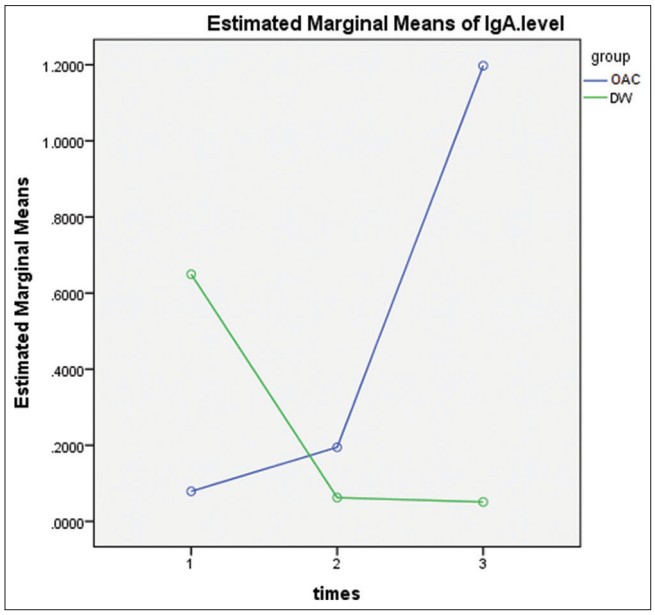

Figure 2: Impact of the two interventions during the studied times (1st, 8th and 15th days of birth) on the urinary IgA levels (OAC group: received oropharyngeal colostrum, DW group: received oropharyngeal distilled water)

Table 2: Urinary IgA levels and clinical outcomes in the two studied groups

Outcomes	OAC group *n*=30	DW group *n*=30	*P*
NEC*	1 (3.3)	3 (10)	0.612
LOS*	8 (26.7)	10 (33.3)	0.779
CLD*	16 (53.3)	14 (46.7)	0.797
Mortality*	1 (3.3)	1 (3.3)	1.00
Length of hospital stay (days)†	39.87±16.64	35.60±15.95	0.315
Time to reach full enteral feeding (days)†	10.70±4.09	10.77±3.79	0.999
Urinary IgA levels†			
1st day after birth	0.15±0.23	0.17±0.35	0.795
8th day after birth	0.19±0.49	0.06±0.08	0.156
15th day after birth	0.39±0.28	0.05±0.10	0.026

*Data are presented as number (%). †Data are presented as mean±SD. OAC group: received oropharyngeal colostrum, DW group: received oropharyngeal distilled water, NEC: necrotizing enterocolitis, LOS: late onset sepsis, CLD: chronic lung disease

In ten other articles, both the clinical outcomes of OAC and its effect on the concentration of immune markers in sterile body fluids such as blood, urine, and saliva of premature infants were investigated; one was retrospective,[15] and the others were RCTs.[5,11,16-22]

Considering various clinical outcomes measured in these studies, OAC was not resulted in statistically significant difference in the incidence of spontaneous intestinal perforation, ventilator- associated pneumonia, retinopathy of prematurity (ROP) and CLD, the days on mechanical ventilation, length of hospital stay, and mortality.[4,12,14-20,22,23]

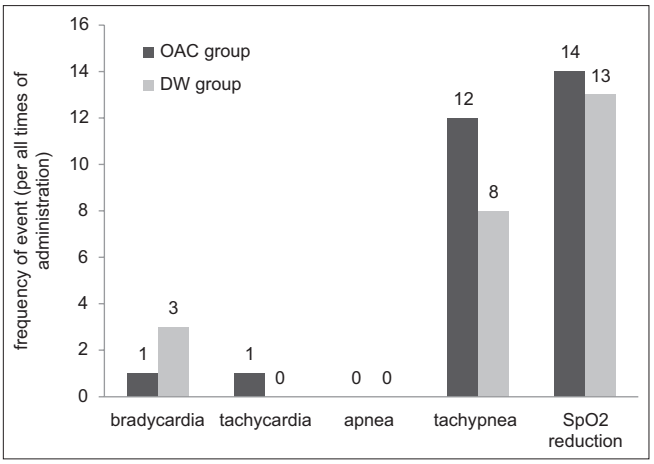

Figure 3: Frequency of adverse events during all times of colostrum or distilled water administration in the two studied groups (OAC group: received oropharyngeal colostrum, DW group: received oropharyngeal distilled water)

Although this was not the case in most of these studies, in three of them, the incidence of feeding intolerance,[21] NEC (especially grade 2 or 3),[13,21] intraventricular hemorrhage (IVH) (grade 3 or 4),[13] and LOS or infections[11,13] was significantly lower in premature infants who received oropharyngeal colostrum. In our study, the incidence of NEC and LOS was lower in this group of infants too, but the difference was not statistically significant; with a larger sample size; the difference might be significant between groups. Here, OAC also had no effect on reducing the incidence of CLD, length of hospital stay, and mortality. Of these studies, one characteristic of the RCT by OuYang X *et al*.[13] with a placebo control group was its large sample size compared to similar RCTs; it makes the results noticeable. It should be noted that in their study, the amount of colostrum administered in each time was more, compared with most other studies including ours; the number of days of its administration was also much more than other studies except one of them.[16] Some studies measured the time to reach full enteral nutrition. In all these studies except one of them, this time was significantly shorter in infants who received oropharyngeal colostrum.[5,13,16,17,20,23] In our study, there was no difference between the two groups in this regard. In the studies which examined the effect of OAC on immune status of premature infants, the concentration of a number of immune markers including sIgA, IgA, IgM, IgG, lactoferrin, interleukin (IL)-1ra, IL-1β, IL-6, IL-8, IL-10, resistin, TNF-α, IFN-γ, and TGE β1 was measured in saliva, urine, blood, or tracheal aspirate at the start of administering oropharyngeal colostrum and in different time intervals between 3 and maximum 30 days thereafter, and different results were obtained. The concentration of sIgA or IgA in the body fluids was measured in eight studies; in two of them, the concentration of this marker was measured only in serum[16] or saliva,[18] and in others, it was also measured in urine. In four of these studies, the

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IgA concentration in saliva, urine, blood, and/or tracheal aspirate was not significantly changed with OAC.[5,17,19,22] In the study by Rodriguez NA *et al*.,[5] the sample size was very small (n = 16). Based on the data analysis, he pointed out that if a large sample size was used, the difference in sIgA concentration in urine and tracheal aspirate might be significant between the two groups. In the RCT by Ferreira D.M.L.M. *et al*.,[19] 113 infants with birth weight less than 1500 g and gestational age less than 34 weeks were enrolled; again, with OAC, there was no significant increase in concentration of IgA in urine and serum. In some other studies, this difference was statistically significant. In the RCT by Moreno-Fernandez J *et al*.,[16] 100 premature infants were studied; OAC resulted in a significant increase in serum IgA concentration. As previously mentioned, duration of OAC in this trial was longer compared with all other studies. Lee J *et al*.[11] studied premature infants with gestational age less than 28 weeks and found that the concentration of sIgA in urine was significantly increased with OAC. Chen XC *et al*.,[21] in a study conducted on mechanically ventilated ELBW infants, showed that OAC was associated with a significantly higher concentration of sIgA in airway secretions and urine on the 6th day of birth.

As mentioned above, in most of these studies, urine sample was one of the body fluid samples on which the effect of OAC on the concentration of IgA was investigated. We decided to use urine sample to measure and compare the concentration of IgA too. This was based on some evidence as follows: In several studies, immunoglobulins IgA, sIgA, IgG, and in some cases IgD were found intact in urine as well as their different fragments.[10] Prentice A showed that feeding term infants with breast milk resulted in significantly increased secretion of IgA in urine.[24] In the study by Goldblum R.M. *et al*.[25] on preterm infants, the same results were obtained; the concentration of IgA, lactoferrin, and secretory components was significantly higher in the urine but not in the serum of infants who were fed with breast milk. As shown by Ishiguro Y *et al*.,[26] it was not the case for formula-fed infants. As in some other studies, we considered days 8 and 15 after birth to measure changes in IgA concentration in urine: In the study by Ishiguro Y *et al*.,[26] the concentration of IgA in urine gradually decreased within the first few days of life. On the 7th day of birth, its level started to increase sharply and reached about 100 ng/ml by day 14, suggesting that the majority of sIgA present in urine before day 7 of birth is of maternal origin; measuring its concentration in urine thereafter reflects the production of this immunoglobulin by the infant itself.

Our study showed that the urinary IgA concentration significantly increased on day 15 of birth in the group who received oropharyngeal colostrum; on the contrary, in another group, its concentration decreased on days 8 and 15 compared to the first day of birth. It is noteworthy that only in two studies in which premature infants had increased concentration of sIgA in urine and/or airway secretions with OAC, they simultaneously had less common morbidities of prematurity.[11,21] Thus, the role of increased concentration of this immune marker and other anti-inflammatory markers in body fluids of premature infants in improvement of their clinical outcomes is not clear yet.

Between 2018 and 2021, several systematic reviews and meta-analyses have been conducted on existing studies, but in most of them, the results regarding the effect of OAC on the concentration of immune markers and/or clinical outcomes of premature infants have been inconclusive and for some reasons including a small number of studies, small sample sizes in most of them, and low quality of the evidence, its overall effectiveness has been found to be uncertain.[23,27-29] The differences in starting time of OAC, number of times of administration per day and amount of colostrum administered in each time, the number of days of administration, gestational age, and birth weight of enrolled infants can also affect the results. In the study by Maffei D *et al*.,[30] there was a direct relationship between the number of doses of oropharyngeal colostrum administered within the first 72 hours of birth and the increase in urinary IgA concentration. In our study, the administration of oropharyngeal colostrum was continued for 72 hours, similar to most existing studies. It is suggested to design studies in which oropharyngeal colostrum is administered for a longer period of time and enteral nutrition is also started as soon as possible to find how simultaneous oropharyngeal and enteral administration of colostrum for a while could synergistically affect the immune status of premature infants and especially reduce the incidence of their common morbidities such as LOS and NEC. Also, considering mean gestational age and birth weight of the infants in our study, we recommend that further trials are designed in which only extremely low gestational age neonates (ELGANS) who have more diminished innate immunity and more attenuated immune responses and accordingly are more susceptible to abovementioned morbidities are studied.

The sample size in our study was not large enough; it may partly explain why the frequency of common morbidities of these preterm infants was not significantly different between the two groups.

Administration of oropharyngeal colostrum to premature infants within the first days of life, as named oral care by some authors, could be recommended yet, regarding its feasibility and lack of adverse effects.

Conclusions

Oropharyngeal administration of colostrum within the first days of life in preterm infants increases the concentration

of IgA in urine. The impact of this immune response on common morbidities of these infants, particularly ELGANS, still needs to be investigated more in other larger studies.

Key message

Considering the effect of administration of oropharyngeal colostrum on immune responses of preterm infants, it is valuable that larger studies are designed, particularly on extremely low gestational age neonates, to investigate its impact on their common morbidities.

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Conflicts of interest

There are no conflicts of interest.

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