

Association of oropharyngeal colostrum administration with decreased inflammatory indices in premature newborns weighing less than 1500 g

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Abstract

Background: The administration of colostrum through its absorption at the oropharyngeal level stimulates the mucosa-associated lymphoid tissue, providing a local immunological protection barrier. The study aimed to investigate the association of oropharyngeal colostrum administration with the reduction of inflammatory indices. **Materials and methods:** This was an observational, ambispective, analytical study of newborns < 32 weeks of gestation at risk of sepsis. Oropharyngeal colostrum was administered at 0.2 mL every 4 h for 5 days. Inflammatory indices were analyzed. Statistical analysis included frequencies, percentages, mean and Standard deviation, contingency coefficient, and Kolmogorov–Smirnov test for the distribution curve of the numerical data. **Results:** There were 50 patients, 33 (66%) female and 17 (34%) male, with a median gestational age of 30-31 weeks (95% confidence interval [CI]). Nineteen patients had sepsis. A lower positivity rate in C-reactive protein was found, with a median of 0.5-0.6 (95% CI) at 5 days of colostrum administration versus 0.5-1.1 (95% CI) as the initial C-reactive protein. Analysis with χ^2 yielded a $p = 0.13$, and the contingency coefficient showed a $p = 0.196$, indicating an association. **Conclusion:** Oropharyngeal colostrum administration was associated with a lower C-reactive protein positivity rate and clinical improvement in premature newborns at risk of sepsis.

Keywords: Colostrum. Oropharyngeal. Newborns. Premature. C-reactive protein.

Asociación de la administración de calostro orofaríngeo con la disminución de los índices inflamatorios en recién nacidos prematuros menor de 1500 g

Resumen

Introducción: La administración del calostro a través de su absorción a nivel orofaríngeo estimula el tejido linfóide asociado a mucosas, proporcionando una barrera de protección local e inmunológica. Conocer la asociación de la administración de calostro orofaríngeo con la disminución de los índices inflamatorios. **Material y métodos:** Observacional, ambispectivo, analítico, recién nacidos < 32 semanas de gestación con riesgo de sepsis, se administró calostro orofaríngeo 0.2 ml cada 4 horas durante 5 días. se analizó índices inflamatorios, evolución clínica. Análisis estadístico: frecuencias, porcentajes, media y DS, coeficiente de contingencia y prueba de Kolmogorov Smirnov para la curva de distribución de los datos numéricos. **Resultados:** Fueron 50 pacientes, 33 (66%) femenino, 17 (34%) masculino, edad gestacional mediana 30-31 semanas

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(IC 95%), 19 pacientes cursaron con sepsis encontrando menor índice de positividad en la PCR, mediana de 0.5-0.6 (IC 95%) a los 5 días de administración de calostro vs 0.5-1.1 (IC 95%) como PCR inicial, analizando con Chi cuadrada con valor $p = 0.13$, mediante coeficiente de contingencia con $p = 0.196$, traduciendo asociación. **Conclusión:** La calostroterapia se asoció con menor índice de positividad en la PCR; clínicamente hacia la mejoría, en recién nacidos prematuros con riesgo de sepsis.

Palabras clave: Calostro. Orofaringeo. Prematuro. Recién nacido. Proteína C reactiva.

Introduction

The neonatal period is particularly critical because newborns are immediately exposed to a large number of microorganisms. The high rates of morbidity and mortality observed during the 1st months of life due to infectious diseases are due to, among other factors, significant quantitative deficiencies in various components of the immune system¹. To compensate for this immunological immaturity inherent in the fetal, neonatal, and early months of life, nature has developed adaptive protection mechanisms provided by the mother, represented by transplacental transfer of antibodies, anti-infective resistance factors in amniotic fluid, and colostrum and breast milk in the extrauterine life².

Colostrum, the milk produced during the 1st days after birth, is a rich source of nutrients and contains high concentrations of various protective factors with anti-infective action. These factors include enzymes (lysozyme, lactoferrin, among others), immunoglobulins (Ig), cytokines, components of the complement system, leukocytes, oligosaccharides, nucleotides, lipids, and hormones that interact with each other and with the mucous membranes of the digestive tract and upper respiratory tract of newborns. This interaction provides passive immunity and stimulation for the development and maturation of the immune system³.

The antimicrobial factors in colostrum and milk have some common characteristics, such as resistance to degradation by digestive enzymes, protection of mucosal surfaces, and elimination of bacteria without initiating inflammatory reactions⁴. Recent studies have demonstrated that the colostrum of women who have given birth to a premature newborn has a higher concentration of these defensive factors, suggesting that they have an important biological role in protecting preterm infants, who are at high risk of infection, during the 1st days of life⁵⁻⁷.

The innate immune system comprises physicochemical barriers and non-specific mechanisms such as phagocytosis, inflammation, acute phase proteins, the complement system, natural killer cells, and dendritic cells. Innate immunity plays a fundamental role during

the 1st days of life of the premature neonate, whereas the adaptive immune system develops through the interaction between environmental factors and the mucosal surface⁸. The innate immune system has an immature development that is expressed in an inadequate elimination of bacterial infection and abnormal recruitment of immune cells at the site of infection or inflammation, leading to damage in the host tissue⁹.

Oropharyngeal administration differs from oral administration; it consists of placing small amounts of colostrum (0.2 mL) directly on the oral mucosa with the expectation that the liquid or any of its components will be absorbed by the mucosa. Studies show it is safe, feasible, and well tolerated even by the smallest premature babies¹⁰⁻¹². Oropharyngeal administration of colostrum would be considered a complement, not a substitute for trophic enteral nutrition.

The study performed by Martín et al. (2016) evaluated the effects of oropharyngeal colostrum administration during the first 15 postnatal days on serum IgA levels in very low birth weight preterm newborns during the 1st month of life. The study was an uncontrolled, randomized clinical trial involving 34 newborns. A statistically significant increase in serum IgA levels was found in both the intervention group ($p < 0.001$) and the control group. At 1 month of life, serum IgA levels were significantly higher in the intervention group than in the control group ($p = 0.026$). This study suggests that the administration of oropharyngeal colostrum favors the development of the immune system of preterm and very low birth weight newborns through the increase in IgA at 1 month of life¹³.

The pilot study performed by Sohn et al. (2015) determined that administering the mother's colostrum in the oral cavity in the 1st days of life alters the oral microbiota compared to control newborns. The study shows that the oral microbiota changed remarkably during the 96 h in all the newborns that received colostrum. The study concludes that the buccal administration of maternal colostrum to extremely preterm infants influenced the colonization of the oral cavity, with this difference remaining until 48 h after the end of the intervention¹⁴.

Methods

The study was approved by the Local Committee for Research and Ethics in Health Research No. 1002, registration number R-2021-1002-007. It was carried out from August 1, 2020, to February 28, 2021, at the Neonatal Intensive Care Unit of the High Specialty Medical Unit, Gynecology-Pediatrics Hospital # 48 of the IMSS in León, Guanajuato.

It was an observational, analytical, ambispective study, including premature newborns under 32 weeks of gestation weighing < 1500 g, with risk of sepsis, and with hemodynamic and respiratory stability. Newborns in shock, with perinatal asphyxia, gastrointestinal malformations, and children of mothers with human immunodeficiency virus infection were excluded from the study.

Study overview

After the approval by the Ethics Committee for Health Research and the Local Health Research Committee No. 1002, Dr. Juan Leonel Moreno Saldaña, a 2nd-year resident of Neonatology, went to the neonatal intensive care unit and pathological nursery service, where he reviewed clinical records of premature newborns who met the inclusion criteria. The mothers were explained how to extract breast milk, and the colostrum was administered according to the colostrum protocol of the neonatology division, which consists of administering 0.2 mL of maternal colostrum every 4 h over 5 days. Patients were monitored for systemic inflammatory response syndrome, acute phase reactants, and the presence or absence of sepsis.

The criteria for deciding on early sepsis diagnosis were risk factors, systemic inflammatory response syndrome, positive PCR acute phase reactants, leukocytosis or leukopenia, and positive blood culture.

The sample size was calculated for a finite population (200 newborns) with a confidence level of 90% and a margin of error of 10%, resulting in at least 51 patients.

Statistical analysis

The distribution curve of the numerical data was determined with the Kolmogorov–Smirnov test. Frequencies and percentages were used for descriptive analysis of qualitative variables. For descriptive analysis of quantitative variables, mean and standard deviation were used in the case of a symmetric curve, or medians and ranges in the case of a non-symmetric curve. For inferential

analysis of quantitative variables, Student's t-test was used in the case of a symmetric curve, and the Mann–Whitney U test was used in the case of a non-symmetric curve. The association between the administration of maternal colostrum and the decrease in inflammatory indices was analyzed by contingency coefficient. A value of $p < 0.05$ was considered a value of statistical significance. The data information was analyzed using the statistical package SPSS version 23.0 for tabulation and analysis.

Ethical aspects

According to the regulations of the General Health Law on Research for Health, article 17, the present study has no risk and does not require informed consent. We worked with a vulnerable population, in this case, minors.

This study was reviewed by the Ethics Committee for Health Research and the Local Research Committee of the Gynecology-Pediatrics Hospital of UMAE 48, León, Guanajuato. The benefits for the study participants were a reduction in the risk of complications associated with sepsis, reduced prolonged hospital stays, favoring of the tolerance of the enteral route, and improvement in the immune system of the preterm newborn.

Results

Fifty-one premature newborns were included to whom maternal colostrum was administered. One patient was eliminated for meeting the exclusion criteria (asphyxia), resulting in 50 premature newborns who fulfilled the inclusion criteria. Table 1 describes the general characteristics of the population and the maternal comorbidities.

The characteristics of the studied population were premature newborns with a median gestational age of 30 weeks (95% Confidence interval [CI]) and a weight range of 1080-1215 g (95% CI). Among these newborns, 19 patients were found to have sepsis (with positive C-reactive protein, leukocytosis, and risk factors). Only seven blood cultures were taken, of which one was positive for *Micrococcus* spp., and two were positive for *Staphylococcus aureus* (Table 2). 36% (7) of newborns with early sepsis did not complete 5 days of colostrum administration, whereas 63% (12) of the patients with neonatal sepsis received maternal colostrum for 5 days. A reduction in patients with positive C-reactive protein was observed after 5 days of colostrum administration in those with sepsis, with a median C-reactive protein of 0.5 (95% CI). This was analyzed using the χ^2 test ($p = 0.13$), which did not demonstrate

Table 1. General characteristics of the study population

Variable	Group A (n = 50)	%
Gender F/M, n (%)	33/17	(66/34)
Cesarean section/vaginal delivery, n (%)	47/3	(94/6)
Gestational age (weeks), median (min-max)	30	(30-31)
Birth weight (g), median (min-max)	1140	(1080-1215)
1 min Apgar, median (min-max)	7	6-7
5 min Apgar, median (min-max)	7.4	7-8
Prenatal steroid use, n (%)	28	(55%)
Surfactant use, n (%)	37	(74%)
Day of mechanical ventilation, median (min-max)	5	(0-18)
Days of continuous positive airway pressure, median (min-max)	6	(0-28)
Days of antibiotic treatment, median (min-max)	7	(0-27)
Maternal age, median (min-max)	25	(17-35)
Maternal comorbidities:		
Chorioamnionitis, n (%)	7	(14%)
Urinary tract infection, n (%)	23	(46%)
Premature rupture of membranes, n (%)	12	(24%)
Gestational diabetes/Pre-eclampsia, n (%)	8	(16%)

F/M: female/male; n: number; g: grams; cm: centimeters; (%): percentage; median: (minimum-maximum).

Table 2. Acute phase reactants, blood cultures, days of colostrum therapy, study population

Variable	Medians	%
Leukocytes initial (U/L), median (min-max)	9520	(6230-11540)
Leukocytes at 5 days (U/L), median (min-max)	11490	(10731-15590)
C-reactive protein initial (mg/L), median (min-max)	0.6	(0.5-1.1)
C-reactive protein at 5 days (mg/L), median (min-max)	0.5	(0.5-0.6)
Early sepsis, n (%)	19	(38%)
Blood culture taken, n (%)	7	(14%)
Positive blood culture, n (%)	3	(6%)
Days of colostrum therapy, median (min-max)	5	(3-5)

n: number; (%): percentage; (min-max): minimum-maximum; (mg/L): milligrams per liter; (U/L): Units per liter. C-reactive protein was analyzed by χ^2 ($p = 0.13$).

Table 3. Association between colostrum administration and frequency of sepsis

Variable	< 5 days number	%	5 days Number	%
Sepsis	7	36	12	63.1
No Sepsis	6	18.7	26	81.25

Analyzed using the contingency coefficient ($p = 0.196$).

statistical significance. Figure 1 shows the C-reactive protein levels upon admission, and Figure 2 shows its levels after 5 days of extrauterine life, indicating an evolution with a lower percentage of positive results.

Table 3 presents the analysis using the contingency coefficient, with a result of $p = 0.196$, which suggests a strong association between colostrum administration and sepsis frequency.

Discussion

The present work was an ambispective observational study. We did not have a control group; however, we divided the groups according to the number of days of receiving maternal colostrum: 5 days or ≤ 4 days. With this narrow difference in time, we observed a tendency toward a decrease in the frequency of sepsis.

The administration of oropharyngeal colostrum could be helpful as an immunomodulator during the 1st month of life. The findings of our study also revealed that the C-reactive protein level at 5 days was lower in the group that received colostrum for 5 days compared to the group that received colostrum for < 5 days.

Maternal colostrum is rich in immunoactive components that change dynamically according to the mother's conditions. Oropharyngeal colostrum is rich in immunological substances capable of activating oral and intestinal immunity, protecting the preterm newborn against serious diseases using IgA, which prevents and helps against mucosal surface pathogens, among other benefits. Studies support potential benefits, including for up to 21 days when administered over 7 days¹⁵.

A meta-analysis conducted in Australia in November 2019 describes oropharyngeal colostrum administration as a safe and easy intervention with immunostimulatory effects that may reduce the risk of sepsis and facilitate enteral feeding. Colostrum cytokines stimulate mucosa-associated lymphoid tissue, and breast milk oligosaccharides protect the gastric mucosa and stimulate the production of prebiotics¹⁶.

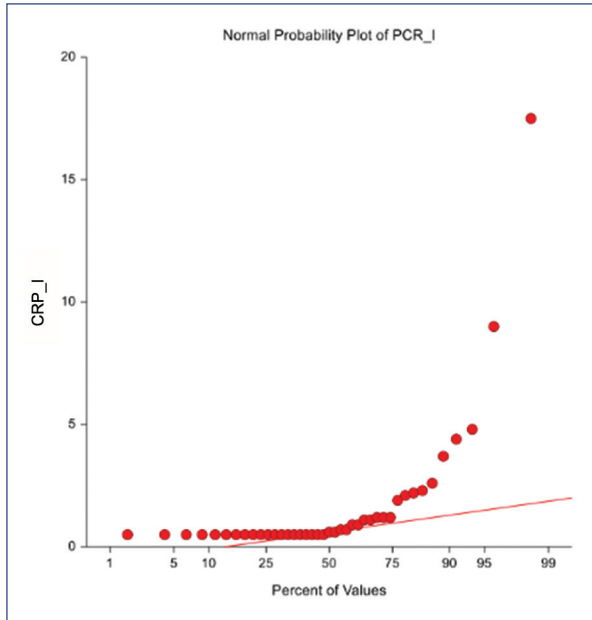


Figure 1. The CRP levels shown were measured upon admission. CRP_I: initial C-reactive protein.

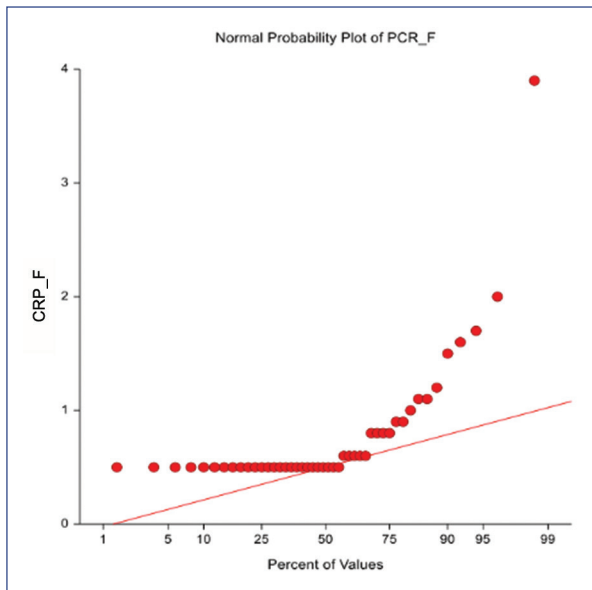


Figure 2. CRP levels at 5 days of extrauterine life, showing an evolution with a lower percentage of positive results, as presented in Table 2 with a median value of 0.5 (95% confidence interval: 0.5-0.6). CRP_F: final C-reactive protein.

In a recent study, Martín-Álvarez et al.¹⁷ conducted research with 100 newborns under 32 weeks of gestation, where they divided them into two groups: (n = 48) in the colostrum group and (n = 52) without oropharyngeal

colostrum. The colostrum group received oropharyngeal colostrum every 4 h for 15 days. Serum concentrations of IgA, IgM, IgG1, lactoferrin, and resistin were measured on days 1, 3, and 15. The study found that IgA and IgM increased in premature newborns who were administered colostrum, and they reached complete enteral nutrition before the control group, without differences between common morbidities. In our study, where an association between sepsis and colostrum administration was analyzed, we found that it was not statistically significant. However, there was a strong association between colostrum administration and decreased sepsis.

Another study reported that those in the group with maternal colostrum had a shorter hospital stay, lower rate of enterocolitis, late sepsis, and even death, suggesting that the administration of oropharyngeal colostrum is recommended for routine administration in the intensive care unit¹⁸. Our study was carried out for 5 days, but it is possible that the benefits mentioned above could be evidenced by expanding the sample and continuing to follow the protocol.

Similar studies have shown that newborns who received maternal colostrum had a shorter hospital stay, a lower rate of enterocolitis, late sepsis, and even death, indicating that the administration of oropharyngeal colostrum is recommended for routine administration in the intensive care unit. In our study, the gestational age was 32 weeks, and our results showed that the C-reactive protein at the study's end was lower than the admission C-reactive protein (95% CI 0.5-0.6 vs. 0.5-1.1). It is advisable to continue monitoring the protocol and expand the sample to obtain a significant statistical value. The clinical evolution of sepsis in our patients was toward improvement, and there were no deaths.

In a meta-analysis of 39 studies comparing procalcitonin versus C-reactive protein as commonly used biomarkers in neonatal sepsis, the authors found greater specificity (82-91%) than sensitivity (89-77%), respectively. They conclude that further studies directly comparing both biomarkers, especially in extremely and very low birth weight infants, are needed to determine their clinical value in guiding antibiotic therapy in neonatal sepsis¹⁹.

The overall quality of the evidence (grades of recommendation, assessment, development, and evaluation analysis) is still very low. Adequately powered clinical trials are needed to confirm nutritional and immunomodulatory benefits in preterm infants²⁰. In our setting, the data analyzed regarding the systemic inflammatory response are limited to clinical findings, C-reactive protein determination, leukocytes, and blood cultures, and a strong downward

trend is observed; however, the short study time and the lack of a control group limit the evidence of the effects of colostrum on the inflammatory process. Secondary outcomes were inadequate. However, as in our study, they conclude a tendency toward a positive and protective effect.

Our unit's study supports that the administration of oropharyngeal colostrum is a beneficial maneuver for premature babies weighing < 1500 g and generates the need to continue expanding research in this field with a greater number of patients.

Strengths: The characteristics of the studied population were very similar; the study was limited to patients younger than 32 weeks and weighing < 1500 g. The trend was toward decreasing sepsis.

Weaknesses: There was no control group, patients with < 5 days of maternal colostrum were included, and the laboratories taken for the sample were limited. The sample size for analysis was limited.

Conclusion

Oropharyngeal colostrum administration was associated with a lower C-reactive protein positivity rate and clinical improvement in premature newborns at risk of sepsis.

Because it is innovative, economical, and safe, it is recommended as the first medical indication for premature newborns in the neonatal intensive care unit.

We found an extensive area of opportunity for conducting clinical trials.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

Conflicts of interest

The authors declare no conflicts of interest.

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