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PROTECTIVE EFFECT OF COLOSTROTHERAPY IN PREMATURE BABIES WEIGHING LESS THAN 1500 G

EFECTO PROTECTOR DE CALOSTROTERAPIA EN PREMATUROS CON PESO MENOR A 1500 G

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ABSTRACT

Introduction: Prematurity is a public health problem due to its high morbidity and mortality. The main causes of mortality in premature infants are associated infections. In Peru, the percentage of premature births increased from 6.4% in 2020 to 7.5% in 2023, with an average of 30,000 premature babies annually. In the National Maternal Perinatal Institute (INMP), of all neonatal deaths by 2023, 70% corresponded to premature babies and 46.5% to those less than 1500 g. **Objective:** Determine the protective effect of colostrotherapy in very low birth weight premature infants at the INMP. **Methods:** An observational, analytical, longitudinal retrospective, cohort study was carried out. We worked with 462 premature babies with very low birth weight, divided into two groups at a ratio of 1:1 for those exposed and not exposed to colostrotherapy. To evaluate its protective effect, three study models were proposed: Model 1, which is necrotizing enterocolitis; model 2, mechanical ventilation and model 3, mortality. A bivariate and multivariate Poisson regression model was used to estimate the crude and adjusted relative risk with their respective 95% confidence intervals. Results: The multivariate analysis showed that colostrotherapy acts as a protective factor for necrotizing enterocolitis (1.73 % vs 7.79 %, aRR: 0.298, 95 %CI: 0.1-0.91) and mortality (12.98% vs 42.86 %, aRR 0.494, 95 %CI: 0.32-0.76); in contrast, the requirement for ventilation therapy did not show a significant association (62.77 % vs 75.32%, aRR 0.92, 95%CI: 0.72-1.2). **Conclusions:** Colostrotherapy is a protective factor for necrotizing enterocolitis and mortality in premature neonates of very low birth weight.

Keywords: Necrotizing enterocolitis; Newborn; Neonate; Calostro; Calostroterapia. (Source: MESH-NLM)

RESUMEN

Introducción: La prematuridad es un problema de salud pública por su alta morbimortalidad. Las principales causas de mortalidad en prematuros son infecciones asociadas. En Perú, el porcentaje de nacimientos prematuros aumentó de 6.4 %, en 2020; a 7.5 %, en 2023, con un promedio de 30 000 prematuros anuales. En el Instituto Nacional Materno Perinatal (INMP), de todas las muertes neonatales para 2023, 70 % correspondieron a prematuros y 46.5 %, a los que tenían menos de 1500 g. **Objetivo:** Determinar el efecto protector de la calostroterapia en prematuros de muy bajo peso al nacer en el INMP. **Métodos:** Se realizó un estudio observacional, analítico, longitudinal, de tipo cohorte retrospectiva. Se trabajó con 462 prematuros de muy bajo peso al nacer, dividido en dos grupos a razón de 1:1 para expuestos y no expuestos a la calostroterapia. Para evaluar su efecto protector, se plantearon tres modelos de estudio: Modelo 1 que es enterocolitis necrotizante; modelo 2, ventilación mecánica y modelo 3, mortalidad. Se trabajó con un modelo de regresión de Poisson bivariado y multivariado para estimar el riesgo relativo crudo y ajustado con sus respectivos intervalos de confianza al 95 %. **Resultados:** En el análisis multivariado, se evidenció que la calostroterapia actúa como factor protector para enterocolitis necrotizante (1.73 % vs. 7.79 %, RRa: 0.298, IC95 %: 0.1-0.91) y mortalidad (12.98% vs. 42.86%, RRa 0.494, IC95%: 0.32-0.76), a diferencia del requerimiento de ventiloterapia que no mostró asociación significativa (62.77 % vs 75.32 %, RRa 0.92, IC95 % 0.72-1.2). **Conclusiones:** La calostroterapia es un factor protector para la enterocolitis necrotizante y mortalidad en neonatos prematuros con muy bajo peso al nacer.

Palabras clave: Recién nacido; Neonato; Calostro; Calostroterapia; Enterocolitis necrotizante. (Fuente: DeCS-BIREME)

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INTRODUCTION

Prematurity is a public health issue due to its high morbidity and mortality [1]; its main causes are necrotizing enterocolitis and late-onset sepsis [2]. Globally, 15 million preterm infants are born annually, of which approximately one million die [3].

In Peru, the number of births in 2020 was 461,735, and in 2023, 410,442, with 6.4% and 7.5% being preterm, and 0.83% and 0.95% being very low birth weight (VLBW) preterm infants, respectively[4]. The neonatal mortality rate for 2021 was 8.8 per 1000 live births (lb), with an average of 5000 neonatal deaths [4]; of the total neonatal deaths in 2023, 70% were preterm infants, and 46.5% were VLBW [5]. At the INMP, 13,555 live births were recorded in 2021, while 12,314 were attended in 2023, with a mortality rate of 14.9 per 1000 lb and 16.5 per 1000 lb, respectively, with 16% being preterm infants and 2.4% VLBW. Of the latter group, 60% of the deaths were neonatal [6].

Transitory immune deficiency in preterm infants is reported; functions such as phagocytosis, cell-mediated immunity, humoral immunity, and complement system development are incomplete. When a preterm infant is born, the transplacental transfer of bioactive elements, such as maternal IgG, as well as naïve and memory T cells, B cells, NK cells, and monocytes, abruptly halts[7-9]. Morbidity and mortality are inversely related to gestational age, with the most common pathologies in preterm infants being hyaline membrane disease, hypoglycemia, intraventricular hemorrhage, neonatal sepsis, necrotizing enterocolitis, anemia, jaundice, patent ductus arteriosus, coagulation disorders, retinopathy, hearing loss, and bronchopulmonary dysplasia; infectious events are most associated with mortality. Additionally, they require assisted ventilation and longer hospitalizations compared to term neonates.

Among the strategies proposed to improve outcomes in preterm infants is colostrum therapy, also known as immune therapy, which involves the administration of colostrum to the oropharyngeal mucosa of the newborn[3,10]. Colostrum contains oligosaccharides that protect the mucosal barrier and stimulate the growth of beneficial bacteria in the mucosa, extracellular vesicles, secretory IgA, lactoferrin, lysozyme, cytokines, leukocytes, stem cells, and microRNA (miRNA), transferring active immune compounds with immediate effectiveness compared to transitional or mature milk, with higher concentrations [3,7,11,12]. Sudeep et al. found a protective effect against late-onset sepsis with the use of colostrum therapy compared to placebo (22.7% vs. 43.3%, RR: 0.73; 95% CI: 0.57-0.9)[8]. Ou Yang et al. determined a protective effect of this intervention against necrotizing enterocolitis (2.36% vs. 10.4%, RRa: 0.23; 95% CI: 0.06-0.84) and late-onset sepsis (4.72% vs. 13.6%, RRa: 0.36; 95% CI: 0.14-0.95)[13].

This study aims to determine the protective effect of colostrum therapy in very low birth weight preterm infants for late-onset sepsis, necrotizing enterocolitis, days on mechanical ventilation, and achievement of full enteral feeding using three statistical models, thus supporting its use as a cost-effective measure to reduce morbidity and mortality in this specific population.

METHODS

Study design

This is an analytical observational longitudinal cohort study, with a retrospective cohort design, conducted in the Neonatology Department of INMP.

Population and sample

The population consisted of very low birth weight preterm infants hospitalized in the Intensive Care, Intermediate Neonatal Care, and Immediate Attention services of the Neonatology Department at INMP, a Level III institution, between 2018 and 2021, with the following inclusion criteria: Exposed group: very low birth weight preterm infants who received colostrum during the study period; Unexposed group: very low birth weight preterm infants who did not receive colostrum during the same period. Patients with incomplete clinical records or missing data on study variables, or those born outside the hospital, with diaphragmatic hernia, asphyxia, esophageal atresia, or major congenital malformations were excluded. For sample size calculation, the GRANMO V.7.12 sample size calculator was used, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast. A total of 231 very low birth weight preterm infants were included in both the exposed and unexposed groups, aiming to detect a minimum relative risk of 0.3, with a disease rate in the unexposed group of 0.1. The POISSON approximation was used. For cohort selection, simple random sampling was performed using an Excel 2016 random

number generator for the clinical records of both groups.

Variables and instrument

To meet the study's objectives, variables were grouped into three segments: obstetric history (number of pregnancies, preeclampsia and/or hypertensive disorders of pregnancy, premature rupture of membranes, chorioamnionitis, urinary tract infection, vulvovaginitis, and third-trimester bleeding), neonatal characteristics (sex, weight, gestational age, minimal enteral nutrition within the first 5 days of life, and administration of colostrum therapy), and neonatal pathologies (early sepsis, late-onset sepsis, necrotizing enterocolitis, mechanical ventilation requirement, days on mechanical ventilation, congenital malformations, days of hospital stay, and discharge condition). Quantitative data on colostrum therapy administration included the age at treatment initiation, number of doses on the first, second, and third days, and the average dose volume each day. Data was collected using a data sheet from selected clinical records based on the sample.

Procedures

The data recorded in the instrument were entered into a database structured in Excel 2016 to ensure no errors. The database was then exported to SPSS-22 for univariate and bivariate analysis. For multivariate analysis, data was entered into STATA16.

Statistical analysis

Descriptive analysis was performed on qualitative and quantitative variables. For quantitative variables, central tendency measures (mean) were calculated. For qualitative variables, frequencies and percentages were determined. Bivariate analysis assessed the association between these variables and the administration of colostrum therapy. Inferential analysis was conducted to demonstrate associations between quantitative variables using the parametric Student's t-test for normally distributed data or the non-parametric Mann-Whitney U test otherwise. For qualitative variables, the Chi-square test was used, with p-values < 0.05 considered significant.

For multivariate analysis, variables that showed a significant association were used. Three study models were proposed (model 1: necrotizing enterocolitis, model 2: mechanical ventilation requirement, and model 3: mortality). To study the degree of association of colostrum's protective factors in each model, relative risk and corresponding 95% confidence intervals (CI) were determined. Variables that were statistically significant in the bivariate analysis were further analyzed using Poisson multiple logistic regression, indicating adjusted relative risk and corresponding 95% CIs.

Ethical considerations

This study followed the ethical considerations of the Taipei Declaration for health database studies. The results will be used solely for the benefit of society; the protection of privacy and confidentiality of the clinical data collected has been ensured. Data collection, storage, and implementation were conducted exclusively by the study team to verify transparency and ensure academic use only.

Additionally, this research was reviewed and approved by the Institutional Ethics Committee for Research and the Functional Research Unit of INMP.

RESULTS

A total of 462 neonates were included in the study. A descriptive analysis was performed for both the exposed and unexposed groups to characterize them and determine the frequencies of each variable. In the exposed group, 43.1% of primigravidae received colostrum therapy, while in the unexposed group, 56.9% were primigravidae, with no significant difference between the two groups ($p = 0.063$). The presence of preeclampsia and/or hypertensive disorders of pregnancy showed a significant difference between the groups; 42.1% of newborns with this maternal history received colostrum therapy ($p = 0.037$). Maternal history of premature rupture of membranes, chorioamnionitis, urinary tract infection, and vulvovaginitis did not show significant differences between the groups ($p > 0.05$).

However, third-trimester bleeding showed a significant difference, with 13.6% of those with this history receiving therapy compared to 86.4% in the unexposed group ($p < 0.01$).

Regarding neonatal characteristics, no significant difference was found between the sexes in both groups ($p = 0.226$), but there was a significant difference in birth weights ($p = 0.037$). Colostrum therapy was administered to 39.1% of neonates with a gestational age (GA) of 28 weeks or less, 53.4% between 29 and 32 weeks, and 57.1% with a GA greater than 32 weeks (p-value: 0.008). Concerning enteral nutrition, an association was observed with colostrum therapy administration ($p < 0.01$), with 60.1% of neonates receiving early enteral nutrition also receiving colostrum therapy. In terms of neonatal pathologies, early sepsis and late-onset sepsis did not show an association with colostrum therapy ($p > 0.05$). However, the development of necrotizing enterocolitis and the need for mechanical ventilation were associated with colostrum therapy administration ($p = 0.002$ and 0.004, respectively). Neither the number of days on mechanical ventilation nor the presence of congenital malformations showed a significant association with the intervention ($p > 0.05$). However, the number of days in the hospital and discharge status were significantly associated with colostrum therapy administration (both $p < 0.01$). In the unexposed group, 76.7% of the neonates died (see Table 1).

Table 1. Association between colostrum therapy administration and neonatal characteristics in very low birth weight preterm infants at INMP, 2018-2021.

Neonatal Characteristics		Colostrum Therapy					
		Yes	%	No	%	Total	p-value
Number of pregnancies	Primipara	56	43.1	74	56.9	130	0.063
	Multipara	175	52.7	157	47.3	332	
Preeclampsia and/or hypertensive	Yes	53	42.1	73	57.9	126	0.037*
disorders of pregnancy	No	178	53	158	47	336	
Premature rupture of membranes	>18 hours	50	48.5	53	51.5	103	0.709
	<18 hours	9	60	6	40	15	
	No	172	50	172	50	334	
Chorioamnionitis	Yes	30	49.2	31	50.8	61	0.891
	No	201	50.1	200	49.9	401	
Urinary infection	Yes	30	44.1	38	55.9	68	0.293
	No	201	51	193	49	394	
Vulvovaginitis	Yes	4	44.4	5	55.6	9	0.736
	No	227	50.1	226	49.9	453	
Third-trimester bleeding	Yes	3	13.6	19	86.4	22	0.000*
	No	228	51.8	212	48.2	440	

Sex	Male	106	47.1	119	52.9	225	0.226
	Female	125	52.7	112	47.3	237	
Weight	<750 g	16	35.6	29	64.4	45	0.037*
	750 g -999 g	43	43	57	57	100	
	1000 g -1249 g	73	52.1	67	47.9	140	
	1250 g -1500 g	99	55.9	78	44.1	177	
Gestational age	≤28 w	54	39.1	84	60.9	138	0.008*
	29 w - 32 w	117	53.4	102	46.6	219	
	>32 w	60	57.1	45	42.9	105	
Minimal enteral nutrition within	Yes	194	60.1	129	39.9	323	0.000*
the first 5 days	No	37	26.6	102	73.4	139	
Early sepsis	Yes	140	47.9	152	52.1	292	0.247
	No	91	53.5	79	46.5	170	
Late-onset sepsis	Yes	116	47.7	127	52.3	243	0.305
	No	115	52.5	104	47.5	219	
Necrotizing enterocolitis	Yes	4	18.2	18	81.8	22	0.002*
	No	227	51.6	213	48.4	440	
Mechanical ventilation	Yes	145	45.5	174	54.5	319	0.004*
	No	86	60.1	57	39.9	143	
Days on mechanical ventilation	1 to 3	43	43	57	57	100	0.812
	4 to 8	29	43.9	37	56.1	66	
	9 to 20	39	50.0	39.0	50.0	79	
	21 to 86	34	45.3	41.0	54.7	75	
Congenital malformations	Yes	24	45.3	29	54.7	53	0.465
	NO	207	50.6	202	49.4	409	
Hospital stay	1 to 21	25	21.6	91	78.4	116	0.000*
	22 to 39	71	60.7	46	39.3	117	
	40 to 55	65	55.6	52.0	44.4	117	
	56 to 219	70	62.5	42.0	37.5	112	
Discharge condition	Deceased	30	23.3	99	76.7	129	0.000*
	Alive	201	60.4	132	39.6	333	

Source: INMP

Subsequently, a descriptive analysis of the quantitative variables of the 231 neonates who received colostrum therapy was conducted. The average age at the start of colostrum therapy was 23.85 hours, with a median of 22 hours, a minimum age of 2 hours, and a maximum of 72 hours. A total of 130 (56.3%) neonates started colostrum therapy before 24 hours of life; 85 (36.8%) started between 24 and 48 hours, and 16 (6.9%) between 48 and 72 hours. On the first day of colostrum therapy, neonates received an average of 2.24 doses, with an average volume of 0.935 ml per dose. The minimum number of doses was 1, and the maximum was 12, with a minimum volume per dose of 0.1 ml and a maximum of 3.8 ml. A total of 66.7% (154 neonates) received between one and two doses on the first day, while 33.3% (77 neonates) received more than two doses. On the second day, 104 neonates received colostrum therapy, with an average of 2.49 doses and an average volume of 1.06 ml. The number of doses ranged from one to eight, with a minimum volume of 0.2 ml and a maximum of 4 ml. A total of 37 (35.6%) neonates received one dose, while 67 (64.4%) received more than one dose. Only 17 neonates received colostrum therapy on the third day. The average number of doses was 2.94, and the average volume was 1.1 ml. Nine (52.9%) neonates received between one and two doses, while eight (47.1%) received more than two doses. Five (29.4%) neonates received less than 1 ml, while 12 (70.6%) received 1 ml or more (see Table 2). It is important to note that colostrum intake was not associated with any adverse events in the neonates.

Table 2. Descriptive analysis of colostrum therapy administration in very low birth weight preterm infants at INMP, 2018-2021.

Mode of administration of colostrum therapy	Start n (%)	First day n (%)	Second day n (%)	Third day n (%)
Age (hours of life)				
<24h	130 (56.3%)			
24-48h	85 (36.8%)			
48-72h	16 (6.9%)			
Number of doses				
1 to 2		154 (66.67%)	37 (35.6%)	9 (52.9%)
>2		77 (33.33%)	67 (64.4%)	8 (47.1%)
Dose volume (ml)				
<1ml		52 (22.5%)	23 (22.1%)	5 (29.4%)
>1ml		179 (77.5%)	81 (77.9%)	12 (70.6%)

Source: INMP

Three regression models were designed: Model 1 focused on necrotizing enterocolitis (NEC); Model 2 examined the requirement for mechanical ventilation (MV); and Model 3 analyzed mortality, aiming to calculate the risk associated with each variable and the model as a whole.

Model 1: Gestational age (< 28 weeks: RR: 2.28, 95% CI: 0.63-8.22 and 29 to 32 weeks: RR: 0.72, 95% CI: 0.02-25.75), the number of colostrum doses on the first day (RR: 0.5, 95% CI: 0.072-3.482), minimal enteral nutrition (RR: 1.15, 95% CI: 0.459-2.871), early sepsis (RR: 1.979, 95% CI: 0.744-5.269), and hospital stay (1 to 21 days: RR: 1.24, 95% CI: 0.13-11.41; 22 to 39 days: RR: 0.27, 95% CI: 0.04-1.62; 40 to 55 days: RR: 0.55, 95% CI: 0.1-3.01) showed no significant association with necrotizing enterocolitis (NEC). Nevertheless, 22.2% of neonates with a maternal history of vulvovaginitis developed

NEC, increasing the risk of NEC by 5.03 times (95% CI: 1.378-18.38). Additionally, 22.7% of infants with a third-trimester bleeding history developed NEC, increasing the risk by 5.882 times (95% CI: 2.39-14.476). A birth weight below 750 g significantly increased the risk of NEC (RR: 5.9, 95% CI: 1.7-20.44). Only 1.73% of neonates who received colostrum therapy developed NEC, compared to 7.79% in the unexposed group. Colostrum therapy acts as a protective factor against NEC development (RR: 0.222, 95% CI: 0.076-0.647). Delayed initiation of colostrum therapy (48-72 hours) increased the risk of NEC (RR: 16.23, 95% CI: 1.34-196.57). Among neonatal pathologies, late-onset sepsis (RR: 18.926, 95% CI: 2.56-139.5) and the need for mechanical ventilation (RR: 9.414, 95% CI: 1.279-69.307) significantly increased the risk. Hospital stay was not associated with an increased risk of NEC.

Model 2: The history of third-trimester bleeding (RR: 1.126, 95% CI: 0.89-1.424) and the age of colostrum therapy initiation (24-48 hours: RR: 1.19, 95% CI: 0.96-1.48; 48-72 hours: RR: 0.84, 95% CI: 0.39-1.83) did not show a significant association with the need for mechanical ventilation (MV). Lower birth weight significantly increased the risk of requiring MV (below 750 g: RR: 1.74, 95% CI: 1.34-2.26; 750 to 999 g: RR: 1.91, 95% CI: 1.6-2.27; 1000 to 1249 g: RR: 1.5, 95% CI: 1.24-1.81). Gestational age less than 28 weeks increased the risk of requiring MV (RR: 2.32, 95% CI: 1.89-2.84), as did gestational age between 29 and 32 weeks (RR: 1.88, 95% CI: 1.5-2.34).

Colostrum therapy was a protective factor against MV (RR: 0.833, 95% CI: 0.736-0.943), with 62.77% of neonates who received colostrum therapy requiring MV, compared to 75.32% of those unexposed. A higher number of doses on the first day reduced the risk of MV (RR: 0.88, 95% CI: 0.674-0.993). Minimal enteral nutrition within the first five days was also a protective factor (RR: 0.806, 95% CI: 0.718-0.906). Among neonatal pathologies, early sepsis (RR: 1.275, 95% CI: 1.106-1.47), late-onset sepsis (RR: 1.345, 95% CI: 1.181-1.531), and NEC (RR: 1.409, 95% CI: 1.26-1.576) significantly increased the risk of requiring MV. A hospital stay of less than 56 days was a protective factor against the need for MV (1 to 21 days: RR: 0.84, 95% CI: 0.74-0.95; 22 to 39 days: RR: 0.53, 95% CI: 0.4-0.64; 40 to 55 days: RR: 0.67, 95% CI: 0.58-0.78).

Model 3: A history of vulvovaginitis (RR: 1.611, 95% CI: 0.764-3.395), the number of colostrum therapy doses on the first day (RR: 1.643, 95% CI: 0.738-3.658), and late-onset sepsis (RR: 0.834, 95% CI: 0.662-1.118) did not show a significant association with discharge outcomes. 68.2% of neonates with a history of third-trimester bleeding died, increasing the risk of death by 2.437 times (95% CI: 1.899-3.647). Lower birth weight significantly increased the risk of neonatal mortality (below 750 g: RR: 8.66, 95% CI: 5.48-13.7; 750 to 999 g: RR: 6.14, 95% CI: 3.93-9.59; 1000 to 1249 g: RR: 2.45, 95% CI: 1.36-4.43). A total of 56.5% of neonates with a gestational age of less than 28 weeks died, showing a 4.94 times higher risk of death compared to those older than 32 weeks (95% CI: 3.17-7.69). Only 12.98% of neonates who received colostrum therapy died, demonstrating a protective factor for discharge outcomes (RR: 0.303, 95% CI: 0.21-0.44).

Late initiation of colostrum therapy (24 to 48 hours: RR: 3.06, 95% CI: 1.43-6.57) increased the risk of death. Minimal enteral nutrition within the first five days was another protective factor (RR: 0.255, 95% CI: 0.19-0.343). Early sepsis (RR: 1.5, 95% CI: 1.08-2.1), NEC (RR: 2.435, 95% CI: 1.71-3.465), and mechanical ventilation (RR: 3.166, 95% CI: 1.949-5.19) significantly increased the risk of death. A hospital stay of 1 to 21 days increased the risk of death by 11.95 times compared to a stay of 56 to 219 days (95% CI: 7.89-18.11) (Table 3)

Table 3. Bivariate analysis between colostrum therapy administration and necrotizing enterocolitis (model 1), mechanical ventilation (model 2), and mortality (model 3) in very low birth weight preterm infants at INMP, 2018-2021.

	MODEL 1 NECROTIZING ENTEROCOLITIS							MODEL 2 MECHANICAL VENTILATION							MODEL 3 MORTALITY						
	YES	%	NO	%	TOTAL	RR	95% CI	YES	%	NO	%	TOTAL	RR	95% CI	YES	%	NO	%	TOTAL	RR	95% CI
RECEIVED COLOSTRUM																					
YES	4	1.7	227	98.3	231	0.2	0.1 - 0.6	154	62.8	86	37.2	231	0.8	0.7- 0.9	30	13	201	87	231	0.3	0.2- 0.4
NO	18	7.8	213	92.2	231			174	75.3	57	24.7	231			99	42.9	132	57.1	231		
VULVOVAGINITIS																					
YES	2	22.2	7	77.8	9	5.0	1.4- 18.4	9	100	0	0	9			4	44.4	5	55.6	9	1.6	0.8 3.4
NO	20	4.4	433	95.6	453			310	68.4	143	31.6	453			125	27.6	328	72.4	453		
THIRD-TRIMESTER BLEEDING																					
YES	5	22.7	17	77.3	22	5.9	2.4- 14.5	17	77.3	5	22.7	22	1.1	0.9-1.4	15	68.2	7	31.8	22	2.4	1.9-3.6
NO	17	3.9	423	96.1	440			302	68.6	138	31.4	440			114	25.9	326	74.1	440		
WEIGHT																					
<750	6	13.3	39	866.7	45	5.9	1.7- 20.4	38	84.4	7	15.6	45	1.7	1.3- 2.3	33	73.3	12	26.7	45	8.7	5.5- 13.7
750-999	8	8	92	92	100	3.5	1.0- 12.6	93	93	7	7	100	1.9	1.6- 2.3	52	52	48	48	100	6.1	3.9- 9.6
1000-1249	4	2.9	136	97.1	140	1.3	0.0- 1.98	102	72.9	38	27.1	140	1.5	1.2-1.8	29	20.7	111	79.3	140	2.5	1.4- 4.4
1250-1500	4	2.3	173	97.7	177			86	48.6	91	51.4	177			15	8.5	162	91.5	177		
GESTATIONAL AGE																					
≤28	12	8.7	126	91.3	138	2.3	0.6- 8.2	122	88.4	16	11.6	138	2.3	1.9- 2.8	78	56.5	60	43.5	138	4.9	3.2- 7.7
29-32	6	2.7	213	97.3	219	0.7	0.0- 25.8	157	71.7	62	28.3	219	1.9	1.5- 2.3	39	17.8	180	82.2	219	1.6	0.8- 3.0
>32	4	3.8	101	96.2	105			40	38.1	65	61.9	105			12	11.4	93	88.6	105		
AGE OF COLOSTRUM THERAPY INITIATION																					
<24H	1	0.8	129	99.2	130			77	59.2	53	40.8	130			9	6.9	121	93.1	130		
24-48H	1	1.2	84	98.8	85	1.5	0.2- 11.1	60	70.6	25	29.4	85	1.2	1.0- 1.5	18	21.2	67	78.8	85	3.1	1.4- 6.6
48-72H	2	12.5	14	87.5	16	16.2	1.3- 196.6	8	50	8	50	16	0.8	0.4- 1.8	3	18.8	13	81.3	16	2.7	0.5-15.0

NUMBER OF DOSES ON THE FIRST DAY																				
1 to 2	2	1.3	152	98.7	154	0.5	0.1- 3.5	90	58.4	64	41.6	154	0.8	0.7-1.0	23	14.9	131	85.1	154	1.6	0.7- 3.7
>2	2	2.6	75	97.4	77			55	71.4	22	28.6	77			7	9.1	70	90.9	77		
MINIMAL ENTERAL NUTRITION WITHIN THE FIRST 5 DAYS																				
YES	16	5	307	95	323	1.2	0.5-2.9	208	64.4	115	35.6	323	0.8	0.7- 0.9	48	14.9	275	85.1	323	0.3	0.2- 0.3
NO	6	4.3	133	95.7	139			111	79.9	28	20.1	139			81	58.3	58	41.7	139		
EARLY SEPSIS																				
YES	17	5.8	275	94.2	292	2	0.7- 5.3	219	75	73	25	292	1.3	1.1- 1.5	93	31.8	199	68.2	292	1.5	1.1- 2.1
NO	5	2.9	165	97.1	170			100	58.8	70	41.2	170			36	21.2	134	78.8	170		
LATE-ONSET SEPSIS																				
YES	21	8.6	222	91.4	243	18.9	2.6- 139.5	191	78.6	52	21.4	243	1.3	1.2- 1.5	62	25.5	181	74.5	243	0.8	0.7- 1.1
NO	1	0.5	218	99.5	219			128	58.4	91	41.6	219			67	30.6	152	69.4	219		
NECROTIZING ENTEROCOLITIS																				
YES								21	95.5	1	4.5	22	1.4	1.3- 1.6	14	63.6	8	36.4	22	2.4	1.7- 3.5
NO								298	67.7	142	32.3	440			115	26.1	325	73.9	440		
MECHANICAL VENTILATION																				
YES	21	6.6	298	93.4	319	9.4	1.3- 69.3								113	35.4	206	64.6	319	3.2	1.9- 5.19
NO	1	0.7	142	99.3	143										16	11.2	127	88.8	143		
HOSPITAL STAY																				
1 to 21	9	7.8	107	92.2	116	1.2	0.1- 11.4	89	76.7	27	23.3	116	0.8	0.7- 0.95	99	85.3	17	14.7	116	12.0	7.9- 18.1
22 to 39	2	1.7	115	98.3	117	0.3	0.0- 1.6	57	48.7	60	51.3	117	0.5	0.4- 0.6	14	12	103	88	117	1.7	0.6- 4.6
40 to 55	4	3.4	113	96.6	117	0.6	0.1- 3.0	71	60.7	46	39.3	117	0.7	0.6- 0.8		6.8	109	93.2	117	1.0	0.6- 1.5
56 to 219	7	6.3	105	93.8	112			102	91.1	10	8.9	112			8	7.1	104	92.9	112		

Source: INMP

Subsequently, we conducted the multivariate analysis. In the first model, the association between colostrum therapy and the presence of necrotizing enterocolitis (NEC) was measured. It was found that the history of vulvovaginitis, birth weight, and the need for mechanical ventilation did not show a significant association with the presence of NEC. However, colostrum therapy (RRa: 0.304, 95% CI: 0.099-0.91) acted as a protective factor against NEC. On the other hand, a history of third-trimester bleeding (RRa: 3.496, 95% CI: 1.19-10.31) and late-onset sepsis (RRa: 14.416, 95% CI: 1.93-109.07) increased the risk of developing NEC. In the second model, the association between colostrum therapy and the use of mechanical ventilation (MV) was analyzed. It was demonstrated that receiving colostrum therapy, birth weight, enteral nutrition, early sepsis, late-onset sepsis, and days of hospital stay were not associated with the need for MV. However, gestational age ≤28 weeks and between 29 to 32 weeks increased the risk of requiring MV (RRa: 1.599, 95% CI: 1.03-2.49 and RRa: 1.589, 95% CI: 1.1-2.3, respectively).

The third model aimed to measure the association between receiving colostrum therapy and mortality. It was found that birth weight, gestational age, early sepsis, and the need for mechanical ventilation did not show a significant association with mortality. However, receiving colostrum therapy (RRa: 0.495, 95% CI: 0.32-0.76) and receiving enteral nutrition (RRa: 0.458, 95% CI: 0.31-0.68) acted as protective factors against mortality (see Table 4).

Table 4. Multivariate analysis for Models 1, 2, and 3 in very low birth weight preterm infants at INMP, 2018-2021.

Variables	Model 1 Necrotizing Enterocolitis			Model 2 Mechanical Ventilation			Model 3 Mortality		
	RR ajustado	IC 95%		RR ajustado	IC 95%		RR ajustado	IC 95%	
Received Colostrum Therapy	0.297	0.1	0.91	0.919	0.72	1.17	0.495	0.32	0.76
Vulvovaginitis	4.112	0.88	19.25						
Third-trimester Bleeding	3.496	1.19	10.31						
Weight									
≤750 G	2.537	0.69	9.29	1.154	0.71	1.88	3.527	1.62	7.68
750-999 G	1.793	0.5	6.46	1.331	0.92	1.93	3.275	1.62	6.63
1000-1249 G	0.855	0.21	3.45	1.230	0.9	1.69	1.877	0.97	3.63
Gestational Age									
≤28 Weeks				1.599	1.03	2.49	1.263	0.58	2.73
29-32 Weeks				1.589	1.1	2.3	0.895	0.44	1.80
Minimal Enteral Nutrition Within First 5 Days				0.914	0.7	1.2	0.458	0.31	0.68
Early Sepsis				1.136	0.89	1.45	1.015	0.67	1.53
Late-onset Sepsis	14.525	1.93	109.07	1.154	0.9	1.47			
Necrotizing Enterocolitis				1.16	0.73	1.85			
Mechanical Ventilation	3.096	0.38	25.11				1.736	0.98	3.07
Hospital Stay									
1-21 Days				0.877	0.62	1.23			
22-39 Days				0.753	0.52	1.08			
40-55 Days				0.776	0.56	1.08			

Source: INMP

DISCUSSION

Of the 462 neonates weighing less than 1500 grams at birth who participated in the study, 231 received colostrum therapy in their first days of life. Despite the extreme prematurity associated with a high comorbidity rate due to their high vulnerability and the strict inverse relationship between weight and gestational age, which is further exacerbated by associated maternal pathologies [14-16], colostrum therapy is among the scientifically evidenced protective strategies. The oligosaccharides in colostrum support immunity, particularly intestinal immunity, modulate helper T cells (Th1/Th2), act on pathogen recognition receptors, possess specific bifidogenic activity, and reduce the growth of pathogenic microorganisms. Additionally, colostrum contains many other molecules, live cells, and even microbes that provide protective effects in neonates[7].

The multivariate analysis showed that colostrum therapy acts as a protective factor against the development of NEC (Bell stage 2 or 3) (RR: 0.222, 95% CI: 0.076-0.647), consistent with findings from OuYang et al. In their randomized controlled trial, they found a 2.36% incidence of NEC in the group that received therapy compared to 10.4% in the placebo group (RR: 0.23, 95% CI: 0.06-0.84)[13]. Similarly, Zhen Yan Fu et al., in a meta-analysis of 16 studies including 1736 neonates, found a statistically significant difference favoring the intervention group for NEC incidence [RR=0.56, 95% CI: 0.38-0.84, Z=2.86, P=0.004] [17], corroborating the findings of other researchers[18].

However, other authors, like Tao et al., did not find a significant association in their meta-analysis regarding NEC incidence (RR = 0.59, 95% CI: 0.33-1.06, p= 0.08)[19]. Similarly, Panchal et al., who reviewed five RCTs, found no significant difference in NEC incidence (RR: 0.83, 95% CI: 0.39-1.75, P = 0.62)[3], and this result has been echoed by others [8,20,21]. The difference in effect could be attributed to variations in the timing of colostrum therapy initiation, the doses administered per day, the total quantity, and the number of days of intervention. Early initiation and higher frequency of administration appear to enhance the protective effect. Regarding mortality, 13% of neonates who received colostrum therapy died compared to 42.8% of those who did not receive it. In the multivariate analysis, colostrum therapy showed a protective effect (adjusted RR: 0.494, 95% CI: 0.32-0.76). Our results align with those of Bashir et al., who conducted a prospective study and found [OR: 0.11, 95% CI: 0.03-0.40] [22]. Additionally, Zhen Yan Fu's meta-analysis of 10 studies showed that the intervention group had a lower incidence of death compared to the control group, and the difference was statistically significant [RR = 0.71, 95% CI: 0.53-0.94, Z=2.38, P = 0.02] [17]. Additionally, Zhen Yan Fu's meta-analysis of 10 studies showed that the intervention group had a lower incidence of death compared to the control group, and the difference was statistically significant [RR = 0.71, 95% CI: 0.53-0.94, Z=2.38, P = 0.02] [23].

Conversely, other authors found no such association, particularly in cases where colostrum therapy was initiated later than 48 hours after birth [3,8,19]. To achieve the greatest benefit from colostrum, there is ongoing debate about the necessary duration of treatment. In our study, neonates received colostrum therapy for three days, with a median of 2.24 doses per day and an average volume of 0.935 ml per dose. There are reports suggesting treatment durations of 8 to 10 days, but no consensus exists, as most patients are typically on minimal enteral nutrition by the third day.

In our study, we found no significant association between colostrum therapy and neonatal sepsis, whether early or late-onset, which is consistent with the findings of other authors [24-26]. However, Lee et al. reported that the incidence of sepsis was lower in the colostrum therapy group compared to the control group (50% vs. 92%, p = 0.03)[27]. Kumar et al., in a meta-analysis of 17 RCTs, found that colostrum therapy significantly reduced the incidence of sepsis (RR = 0.72, 95% CI: 0.56-0.92)[20], corroborating findings from other studies [3,13,17,19,21,23]. Researchers who have found this association typically consider five or more consecutive days of colostrum therapy, suggesting that the duration of therapy may influence this protective effect.

We also found no significant association between colostrum therapy and the duration of mechanical ventilation, similar to Alvarez et al.'s findings [21]. Regarding hospital stay, Tao et al. reported that neonates receiving colostrum had shorter hospital stays (mean difference = −10.38, 95% CI = −18.47–2.29, p = 0.01) [19]. Other authors have found similar associations favoring the intervention (28), while others have reported the opposite [29]. We observed a significant difference in our study, though the longer stays in the exposed group were likely due to the high mortality rate among unexposed neonates.

The main limitations of this study include its execution at a single institution, which may limit the generalizability of the findings, and its retrospective design

CONCLUSION

Oropharyngeal colostrum administration is a simple and safe procedure. This study demonstrated that it acts as a protective factor against necrotizing enterocolitis and mortality in very low birth weight preterm neonates.

ORIGINAL PAPER

Authorship contribution: Carmen Rosa Dávila Aliaga conceptualized, designed the methodology, conducted the research, analyzed the data, drafted the initial and final versions, and reviewed the manuscript. Jean Pierre Eduardo De la Cruz Davila conceptualized, conducted the research, collected the data, analyzed the data, drafted the initial version, and reviewed the manuscript. Brendy Zenia Yancan Riva Conceptualized, conducted the research, collected the data, analyzed the data, drafted the initial and final versions, and reviewed the manuscript. Carmen Rita Villanueva Medina conceptualized, designed the methodology, conducted the research, analyzed the data, drafted the initial and final versions, and reviewed the manuscript. Leidy Melody Villalobos Paz conceptualized, designed the methodology, conducted the research, analyzed the data, drafted the initial and final versions, and reviewed the manuscript. Zulema Frida León Mauricio conceptualized, designed the methodology, conducted the research, analyzed the data, drafted the initial and final versions, and reviewed the manuscript.

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