Bovine Colostrum Supplementation for Prevention of Necrotizing Enterocolitis and Late-Onset Sepsis in Preterm Infants

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Abstract

Background: Necrotizing enterocolitis (NEC) and late-onset sepsis (LOS) continue to be among major causes of significant morbidity and mortality in premature newborns. The purpose of this study was to determine how bovine colostrum supplementation would affect the incidence of NEC and late-onset septicemia in preterm newborns. **Methods:** This is an open-label randomized controlled trial, conducted on 120 preterm infants who were randomly assigned to either the bovine colostrum group (n = 60) or control group (n = 60). Necrotizing enterocolitis, culture proven late onset sepsis, clinically suspected late onset sepsis, feeding intolerance; days to achieving full enteral feeding, days to discontinuing total parenteral nutrition, length of hospital stay and mortality were documented. **Results:** Neonates in the bovine colostrum group had a lower incidence of feeding intolerance, earlier achievement of full enteral intake, shorter duration on parenteral nutrition and shorter hospital stay, achieving a high statistical significance. On the other hand, neonates in the control group had greater frequency of NEC as well as LOS but these differences were not statistically significant. **Conclusion:** The use of bovine colostrum instead of infant formula during the first week of life may reduce the incidence of NEC and LOS in preterm infants. It also reduces the time to achieving full enteral intake, days on parenteral nutrition as well as length of hospital stay.

Key Words: Bovine Colostrum, Necrotizing Enterocolitis, Late-Onset Sepsis, Preterm Infants.

DOI Number: 10.14704/NQ.2022.20.12.NQ77117 **NeuroQuantology 2022; 20(11): 1385-1392**

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Relevant conflicts of interest/financial disclosures:
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Background

Preterm birth is a major contributor of neonatal mortality and morbidity **(Daskalakis, 2019).** Late-onset sepsis (LOS) and necrotizing enterocolitis (NEC) are still among the leading causes of serious morbidity and mortality in preterm infant's inspite of modest reductions over the last decade **(Yi et al., 2018).**

Studies have demonstrated that very low birth weight infants fed with human milk develop fewer sepsis, NEC, and cause less neonatal intensive care unit costs **(Johnson et al., 2015).** Immunoglobulins in human milk reduce the adherence of pathogenic bacteria to the gut epithelium and thus decrease colonization by such bacteria. Other anti-infective factors and growth factors in human milk also play an important role **(Balachandran et al., 2017).** Mother's colostrum or first milk is significantly richer in biologically active peptides, antioxidants, anti-inflammation agents, and growth promoting factors that differ substantially from later milk **(Buttar et al., 2017).**

Unfortunately, maternal colostrum is often in short supply immediately after very preterm birth, and preterm infant formula, designed to mimic maternal milk, is therefore used as the first milk. However, formula remains associated with longer time to full feeding, increased risk of feeding intolerance and NEC, and impaired systemic immunity (e.g., more sepsis) **(Li et al., 2020).** Commercially available bovine colostrum has high concentrations of anti-infective factors such as immunoglobulins, lactoferrin, organism-specific antibodies, lactoperoxidase, insulin-like growth factors and transforming growth factors **(Balachandran et al., 2017).** Bioactive components in bovine colostrum were found to be the most similar to those in maternal milk **(Ahnfeldt et al., 2019).** Moreover, Bovine colostrum is a feasible and low-cost product **(Playford R. J. et al, 2020).**

In view of the above observations, it is hypothesized that bovine colostrum which is a naturally occurring complex mixture of several anti-infective factors could prevent NEC and sepsis.

Aim of this work was to evaluate the effect of bovine colostrum supplementation on prevention of NEC and late onset sepsis in preterm neonates.

Hypothesis: We hypothesized that bovine colostrum supplementation reduces the incidence of NEC and late onset sepsis in preterm infants.

Research Design and Methodology

Study Design and Population:

An open-label randomized controlled trial was conducted including a total of 120 preterm infants (68 Males and 52 Females) who were recruited within the period from February 2020 to February 2021. Included preterm neonates were those admitted to the Neonatal Intensive Care Units of Cairo university hospital and Mataria teaching hospital in the first 24 hours of life, with 28 to 34 weeks gestation. They were randomly assigned into 2 groups, **Group I** (Bovine Colostrum Group) and **Group II** (Control Group), each including 60 preterm infants.

Preterm infants with risk factors including the presence of underlying gastrointestinal problems, severe birth asphyxia, chromosomal abnormalities and structural brain anomalies were excluded from the study. Additionally, preterms with family background of cow milk allergy, suspected congenital infections, early-onset sepsis or any maternal risks for neonatal sepsis e.g., chorio-amnionitis, urinary tract infection or premature rupture of membranes were also excluded.

The study was approved by the Research Ethical Committee of Cairo University hospitals. An informed consent was obtained from legal guardians of each participant before enrollment. A computer-generated random number generator was used to assign the 120 enrolled preterm infants at random in accordance with a specified schedule, either to the group receiving bovine colostrum or to the control group.

Methods

Group l (Bovine Colostrum Group)

This group included 60 preterm neonates who received bovine colostrum (when maternal milk was not available) instead of infant formula until postnasal day 7 and feeding was initiated as soon as possible after birth.

The product used is the first 6 h bovine colostrum present in the form of dry powder to be dissolved in distilled water. It consists of Concentrated immunoglobulins (IgA, IgG, IgM), Lactoferrin, Proline-rich polypeptide, Interferons, Lymphokines, Interleukins, Growth factors (TGFs; TGF-α and TGF-β) and (IGFs; IGF-1, IGF-2) in addition to multiple essential minerals and vitamins.

Bovine colostrum preparation: 10 gms of bovine colostrum powder were mixed in 50 ml cooled previously boiled water, which provides 81 kcal / 100 ml and 8 gm protein / 100 ml. Reconstituted preparation was kept in refrigerator (4°C) for no more than 24 hours. Before use it was warmed to 37°C in a water bath.

Volume: The daily volume of bovine colostrum was determined based on the nutritional guidelines for preterm neonates and feeding policy of the unit, thus, it was initiated as minimal enteral nutrition (10 ml/kg/day) and gradually increased to a maximum of 20 mL/kg/day. After reaching 20 ml/kg/day bovine colostrum, additional feeding volume was added in the form of preterm formula to be subtracted from the total volume of feed for the first 7 days of life.

The protein content in the volume of bovine colostrum administered was not allowed to exceed 3.8–4.4 gm/kg/day for infants <1,000 gm, 3.4–4.2 gm/kg/day for infants 1,000–1,500 gm, based on the American Academy of Pediatrics (AAP) recommendations for enteral protein needs in preterm infants (**Academy of Nutrition Dietetics, 2015).** Thus, when maximum volume of bovine colostrum (due to protein limitations), did not meet the required enteral feeding volume, preterm formula was given to fulfill the missing volume. After the end of intervention study period (First 7 days of life), the infants continued on the preterm formula till discharge, however, when maternal milk became available at any time, the study protocol was discontinued.

Group II (The control group)

This group included 60 preterm neonates who were given infant formula only from the start as a supplementary diet to maternal milk when not available. Initiation of feeding and volume of formula to be fed daily were exactly the same as the Bovine Colostrum Group.

Neonates included in both groups were subjected to full History taking and thorough general and systemic examination. Laboratory tests included Blood culture, CBC with differential count, C-reactive protein (CRP), Random blood sugar (RBS), Serum sodium and Blood gas analysis. Radiological studies in the form of Plain abdominal x-ray (erect and supine views) were done for cases with suspected NEC.

Primary outcomes: Primary outcomes measured comprised frequency of necrotizing enterocolitis, culture-proven LOS and clinically suspected LOS. Necrotizing enterocolitis was diagnosed based on Bells staging system. Culture-proven LOS was confirmed by a microbiological culture of potentially pathogenic bacteria or fungi from blood or cerebrospinal fluid sample collected aseptically after 72 hours of birth, however, clinically suspected LOS was diagnosed using a combination of clinical findings including temperature instability (hypothermia or hyperthermia, respiratory instability (apnea, tachypnea or the need for increased ventilator support), cardiovascular instability (Heart rate >180 or <100 beats/min, hypotension, capillary refill time > 3 seconds), lethargy or altered mental status and feeding intolerance in conjunction with Rodwell hematological scoring system with score (≤2) indicating sepsis is very unlikely, score (3–4) indicating sepsis is suspected and score(≥5) indicating sepsis is more likely.

Secondary Outcomes: Secondary outcomes measured included feeding Intolerance, days to achieve full enteral feeding, days to discontinue total parenteral nutrition and duration of hospitalization, where feeding Intolerance was defined as presence of emesis or gastric residuals exceeding 25% of feeding volume, abnormally enlarged bowel loops presented on physical examination or with an imaging study, diarrhea or visible non-explained blood in the stool for at least 3 consecutive days.

Sample size:

Epi-calc 2000 was used to calculate the sample size of this randomized case control study. Assuming 80% power, 0.05 level of significance, 30% proportion of controls exposed, to detect odds ratio OR=3 and with ratio of cases to controls=1 The sample size is 60 cases & 60 controls with overall 120 preterm neonates.

Statistical analysis:

Microsoft excel 2013 was used for data entry and the statistical package for social science (SPSS) version 21 (SPSS, Armonk, New York: International Business Machines Corporation) was used for data analysis. Simple descriptive statistics (arithmetic mean and standard deviation) used for summary of quantitative data and frequencies used for qualitative data. Bivariate relationship was displayed in cross tabulations and Comparison of proportions was performed using the chi-square

test or fisher exact whenever appropriate. Odds Ration and Confidence interval were used to measure the likelihood of exposure on outcome. T-independent, one-way ANOVA and post-hoc tests were used to compare normally distributed quantitative data. The level of significance was set at probability (P) value <0.05.

Results

There was no significant difference as regards gestational age and birth weight between both groups. Similarly, there was no significant difference in mode of delivery and gender between both groups **(Table 1, 2).**

Based on our clinical data analysis, some clinical manifestations suggestive of sepsis (lethargy, poor suckling and hypothermia) were more pronounced among the control group, with only (lethargy) showing a significant statistical difference (p=0.002), 95% CI (1.519 – 6.756), OR (3.205) **(Table 3).** Also (delayed capillary refill time), was significantly frequent among control group compared to the bovine colostrum group (p=0.002), 95% CI (1.524 – 6.802), OR (3.215) **(Table 4).** Additionally, the frequency of feeding residuals was significantly higher among control group achieving high statistical significance (p<0.001), OR (4.291) and 95% CI (1.956 – 9.433) **(Table 5).**

Regarding lab results, INR (International normalization ratio) values were significantly prolonged (based on reference ranges for gestational age) among control group showing statistical significance (P=0.041), OR (3.039), 95% CI (1.010 - 9.174) **(Table 6).** Although, all haematological parameters involved in rodwell haematological scoring system were more pronounced among control group, this showed no statistically significant difference **(Table 6).** However, there was a significant statistical difference between both groups regarding Rodwell Hematological score ≤ 2 (P=0.017), OR (2.418) and 95% CI (1.160 – 5.039), where more cases had Rodwell Hematological score ≤ 2 in the bovine colostrum group, compared to the control group, indicating that cases of bovine colostrum group were less likely to have a diagnosis of LOS **(Table 7).**

Results of 1ry outcomes showed that incidence of suspected and definite NEC was more frequent among neonates of the control group, but without statistical significance (P = 0.073) and (P = 0.089) respectively. Additionally, no neonates developed advanced NEC in either groups **(Table 8).**

The incidence of culture-proven and clinically-suspected LOS showed no statistically significant difference between both groups (P=0.111) and (P=0.246) respectively. Culture-proven sepsis was documented in 14 neonates (23.3%) of the bovine colostrum compared to 22 neonates (36.7%) of the control group and clinically suspected LOS developed in 9 neonates (15%) of the bovine colostrum group compared to 14 neonates (23.3%) of the control group **(Table 9).**

Results of 2ry outcomes revealed that feeding intolerance was more obvious among the control group showing high statistical significance (P=0.006), OR (3.058) and 95% CI (1.356 - 6.896), where 12 neonates (20%) of the bovine colostrum group developed feeding intolerance versus 26 neonates (43.3%) of the control group **(Table 10).** Additionally, a highly significant statistical difference was recognized between both groups regarding mean days to discontinue TPN (P<0.001), mean days to achieve full enteral feeding (P=0.001) and mean days of hospitalization (P=0.001). Neonates in the bovine colostrum group (Group I) showed markedly less days to discontinue TPN, to achieve full enteral feeding and markedly reduced duration of hospitalization **(Table 11).** Infection-related mortality and all-cause mortality were not significantly different between both groups, where death, occurred in 2 cases (3.3%) in the bovine colostrum group compared to 3 cases (5%) in the control group, and all deaths were secondary to late-onset sepsis **(Table12).**

Table 1: Comparison of gestational age and birth weight in both groups

	Group	N	Mean	Std. Deviation	P value	95% CI Lower	Upper
Gestational age	(Group I)	60	32.17	1.564	0.371	-.342	.908
	(Group II)	60	31.88	1.878		-.342	.908
Birth Weight	(Group I)	60	1.6363	.37975	0.816	-.11516	.14593
	(Group II)	60	1.6209	.34139		-.11518	.14595

Table 2: Comparison of mode of delivery and gender in both groups

		Group						P value	OR	95% CI	
		Group I		Group II		Total				Lower	Upper
		N	%	N	%	N	%				
Mode of Delivery	NVD	12	20.0%	16	27.1%	28	23.5%	0.360	.672	.286	1.578
	CS	48	80.0%	43	72.9%	91	76.5%				
Gender	Male	31	51.7%	37	62.7%	68	57.1%	0.223	.636	.306	1.321
	Female	29	48.3%	22	37.3%	51	42.9%				

Table 3: Comparison of non-specific sepsis manifestations between both groups

		Group						P value	OR	95% CI	
		Group I Cases		Group II Controls		Total				Lower	Upper
		N	%	N	%	N	%				
Lethargy	Yes	21	35.0%	38	63.3%	59	49.2%	0.002	3.205	1.519	6.756
	No	39	65.0%	22	36.7%	61	50.8%				
Poor suckling	Yes	28	46.7%	38	63.3%	66	55.0%	0.067	.507	.244	1.051
	No	32	53.3%	22	36.7%	54	45.0%				
Hypothermia	Yes	3	5.0%	7	11.7%	10	8.3%	0.186	.398	.098	1.621
	No	57	95.0%	53	88.3%	110	91.7%				
Hyperthermia	Yes	0	0.0%	0	0.0%	0	0.0%				
	No	60	100.0%	60	100.0%	120	100.0%				

Table 4: Comparison of cardiovascular manifestations in both groups

		Group						P value	OR	95% CI	
		Group I Cases		Group II Controls		Total				Lower	Upper
		N	%	N	%	N	%				
Tachycardia	Yes	4	6.7%	6	10.0%	10	8.3%	0.509	.643	.172	2.405
	No	56	93.3%	54	90.0%	110	91.7%				
Bradycardia	Yes	2	3.3%	1	1.7%	3	2.5%	0.559	2.034	.180	23.055
	No	58	96.7%	59	98.3%	117	97.5%				
delayed Capillary refill time	Yes	23	38.3%	40	66.7%	63	52.5%	0.002	3.215	1.524	6.802
	No	37	61.7%	20	33.3%	57	47.5%				
Hypotension	Yes	17	28.3%	26	43.3%	43	35.8%	0.087	.517	.242	1.104
	No	43	71.7%	34	56.7%	77	64.2%				

Table 5: Comparison of frequency of feeding residuals in both groups

		Group						P value	OR	95% CI	
		Group I Cases		Group II Controls		Total				Lower	Upper
		N	%	N	%	N	%				
Feeding residuals	Yes	26	43.3%	46	76.7%	72	60.0%	<0.001	4.291	1.956	9.433
	No	34	56.7%	14	23.3%	48	40.0%				

Table 6: Comparison of haematological lab parameters in both groups

		Group						P value	OR	95% CI	
		Group I Cases		Group II Controls		Total				Lower	Upper
		N	%	N	%	N	%				
Leucocytosis - ≥ 25000/mm3 at birth - ≥ 30000/mm3 at 12-24h - ≥21000/mm3 at 2 days	Yes	16	26.7%	20	33.3%	36	30.0%	0.426	.727	.332	1.594
	No	44	73.3%	40	66.7%	84	70.0%				
Leucopenia (≤5,000/µL)	Yes	3	5.0%	9	15.0%	12	10.0%	0.068	.298	.077	1.162
	No	57	95.0%	51	85.0%	108	90.0%				
Decreased PMN count <1800/mm3	Yes	2	3.3%	5	8.3%	7	5.8%	0.439	.379	.071	2.037
	No	58	96.7%	55	91.7%	113	94.2%				
Increased PMN count >5400/mm3	Yes	24	40.0%	27	45.0%	51	42.5%	0.580	.815	.395	1.682
	No	36	60.0%	33	55.0%	69	57.5%				
Increased Immature PMN count	Yes	34	56.7%	33	55.0%	67	55.8%	0.854	1.070	.520	2.200
	No	26	43.3%	27	45.0%	53	44.2%				
I:T ratio > 0.2	Yes	29	48.3%	31	51.7%	60	50.0%	0.715	.875	.428	1.791
	No	31	51.7%	29	48.3%	60	50.0%				
I:M ratio ≥ 0.3	Yes	18	30.0%	28	46.7%	46	38.3%	0.060	.490	.231	1.037
	No	42	70.0%	32	53.3%	74	61.7%				
Thrombocytopenia (<150 × 109/L)	Yes	10	16.7%	19	31.7%	29	24.2%	0.055	2.314	0.970	5.524
	No	50	83.3%	41	68.3%	91	75.8%				
International normalization ratio (INR)	Prolonged	5	8.3%	13	21.7%	18	15.0%	0.041	3.039	1.010	9.174
	Normal	55	91.7%	47	78.3%	102	85.0%				

Table 7: Comparison of Rodwell Hematological score in both groups.

		Group						P value	OR	95% CI	
		Group I (Cases)		Group II (Controls)		Total				Lower	Upper
		N	%	N	%	N	%				
Rodwell Hematological score less or equal ≤ 2	Yes	35	58.3%	22	36.7%	57	47.5%	0.017	2.418	1.160	5.039
	No	25	41.7%	38	63.3%	63	52.5%				
Rodwell Hematological score 3-4	Yes	6	10.0%	12	20.0%	18	15.0%	0.125	.444	.155	1.276
	No	54	90.0%	48	80.0%	102	85.0%				
Rodwell Hematological score ≥ 5	Yes	16	26.7%	23	38.3%	39	32.5%	0.172	.585	.270	1.268
	No	44	73.3%	37	61.7%	81	67.5%				

Table 8: Comparison of the incidence of different stages of NEC between both groups

		Group						P value
		Group I (Cases)		Group II (Controls)		Total		
		N	%	N	%	N	%	
Suspected NEC stage IA or IB	IA	8	13.3%	7	11.7%	15	12.5%	0.073
	IB	0	0.0%	5	8.3%	5	4.2%	
	No	52	86.7%	48	80.0%	100	83.3%	
Definite NEC IIA or IIB	IIA	3	5.0%	5	8.3%	8	6.7%	0.089
	IIB	0	0.0%	4	6.7%	4	3.3%	
	No	57	95.0%	51	85.0%	108	90.0%	
Advanced NEC IIIA or IIIB	No	60	100.0%	60	100.0%	120	100.0%	

Table 9: Comparison of the incidence of culture-proven and clinically suspected LOS between both groups

		Group						P value	OR	95% CI	
		Group I (Cases)		Group II (Controls)		Total				Lower	Upper
		N	%	N	%	N	%				
Culture proven LOS	Yes	14	23.3%	22	36.7%	36	30.0%	0.111	.526	.237	1.165
	No	46	76.7%	38	63.3%	84	70.0%				
Clinically suspected LOS	Yes	9	15.0%	14	23.3%	23	19.2%	0.246	.580	.229	1.466
	No	51	85.0%	46	76.7%	97	80.8%				

Table 10: Comparison of incidence of feeding intolerance between both groups

		Group						P value	OR	95% CI	
		Group I (Cases)		Group II (Controls)		Total				Lower	Upp
		N	%	N	%	N	%				
Feeding intolerance	Yes	12	20.0%	26	43.3%	38	31.7%	0.006	3.058	1.356	6.89
	No	48	80.0%	34	56.7%	82	68.3%				

Table 11: Comparison of days to discontinue total parental nutrition (TPN), achieve full enteral feeding and duration of hospitalization between both groups.

	Group	N	Mean	Std. Deviation	P value	95% CI Lower	Upper
Days to discontinue TPN	Group I (Cases)	60	11.82	6.917	<0.001	-8.141	-2.359
	Group II (Controls)	60	17.07	8.946		-8.143	-2.357
Days to achieve full enteral feeding	Group I (Cases)	60	18.07	8.649	0.001	-9.973	-2.696
	Group II (Controls)	60	24.40	10.931		-9.983	-2.686
Duration of hospitalization	Group I (Cases)	60	23.85	10.996	0.001	-12.955	-3.245
	Group II (Controls)	60	31.95	15.483		-12.960	-3.240

Table 12: Comparison of mortality between both groups

		Group						P value	OR	95% CI	
		Group I (Cases)		Group II (Controls)		Total				Lower	Upper
		N	%	N	%	N	%				
Infection-related mortality	Yes	2	3.3%	3	5.0%	5	4.2%	0.648	.655	.106	4.069
	No	58	96.7%	57	95.0%	115	95.8%				
All cause mortality	Yes	2	3.3%	3	5.0%	5	4.2%	0.648	.655	.106	4.069
	No	58	96.7%	57	95.0%	115	95.8%				

Discussion

Our results show reduction in NEC development among neonates of bovine colostrum group. Also, there was a difference in severity of definite NEC episodes, as all 3 cases of bovine colostrum group were stage IIA with none progressing to stage IIB, while in the control group 5 cases (8.3%) were stage IIA while 4 cases (6.7%) progressed to stage IIB, however, these differences didn't reach statistical significance (P=0.089). Similarly, **Ismail et al. (2021),** showed that gut priming with bovine colostrum was associated with reduced incidence of NEC compared to placebo group but without statistical significance. On the contrary, **Balachandran et al. (2017),** showed no difference in the occurrence of NEC between bovine colostrum group versus placebo group, even revealed a trend toward higher stool IL-6 levels and increased incidence of radiological features of NEC in the bovine colostrum group. This conflicting result may be related to their use of a different product with different doses and dilutions **(Balachandran et al., 2017).** In our study, none of the neonates in both groups developed advanced NEC, which was comparable to results of **Juhl et al. (2018),** as they reported no occurrence of surgical NEC.

Analyzing the effect of bovine colostrum on LOS, we noticed reduced sepsis episodes among bovine colostrum group compared to the control group, however, these differences were not statistically significant as regards culture proven sepsis or clinically suspected sepsis. Remarkably, there was a statistically significant difference in number of neonates who acquired a Rodwell Hematological score ≤ 2, 35 cases in the bovine colostrum group, versus 22 cases in the control group (p value= 0.017), which signals a trend towards clinical sepsis diagnosis being less likely among bovine colostrum cases.

Moreover, our statistical analysis revealed that some clinical manifestations suggesting neonatal sepsis were markedly prominent among the control group compared to the bovine colostrum group. These include lethargy (p=0.002), delayed capillary refill time (p=0.002), feeding residuals (p<0.001), elevated INR (p=0.041) suggesting more pronounced clinical picture of sepsis among the control group.

Our results were approximating to previous studies, where **Ismail et al. (2021)** noticed fewer sepsis episodes with the use of bovine colostrum that didn't reach statistical significance. They did however find, significantly lower severity of sepsis episodes with bovine colostrum. Similarly, **Balachandran et al. in (2017),** detected fewer cases with definite sepsis in the bovine colostrum group than the control group but also without statistical significance. Moreover, **Sadeghirad et al. (2018)** reported that infants who received colostrum were at less risk of developing sepsis than those receiving a placebo or usual care. Remarkably, initial results of phases A and B of the

Precolos, (2017) revealed no diagnosis of sepsis in infants who received bovine colostrum **(Li et al., 2017).** So, the cumulative results of these studies, like ours show a trend towards less incidence of sepsis and NEC, even if failed to reach statistical significance.

Reviewing literature, several small studies revealed reduction in late-onset sepsis (LOS) in preterm infants supplemented with bovine lactoferrin (as a constituent of bovine colostrum) **(Pammi and Suresh, 2017) but** these results were not replicated when a recent large randomised controlled trial (RCT) of over 2200 infants was conducted **(Griffiths et al., 2019).** This may suggest that using bovine colostrum as a whole, taking advantage of all of its bioactive factors may result in more pronounced effects against infection and NEC in newborns.

These recognized effects of bovine colostrum in reducing the risk of NEC and late onset neonatal sepsis, may be related to its bacteriostatic substances, including, immunoglobulins, lactoperoxidase, lactenins, lactoferrins, lysozymes, and leukocytes **(Wasowska and Puppel, 2018).** These constituents are involved in modulating the immune system and targeting microbes **(Playford and Weiser, 2021).**

Achieving full-enteral feeding in a shorter period of time relates to an earlier removal of central lines, less days on total parenteral nutrition and, perhaps, to less associated infections. Our study emphasized that cases of bovine colostrum group reached full enteral feeding much earlier than those of the control group, which was statistically significant (p=0.001). Also feeding intolerance was significantly reduced among bovine colostrum cases compared to the control group, where 12 cases (20%) of the bovine colostrum group developed feeding intolerance compared to 26 cases (43.3%) in the control group (p=0.006).

This may be attributed to the fact that BC has repeatedly been shown to stimulate gut maturation **(Rasmussen et al., 2016).** Therefore, the faster advancement in enteral feeding may be due to improved intestinal maturation, evidenced by the observation of less feeding intolerance.

Regarding the effect of bovine colostrum on feeding intolerance, **Juhl et al. (2018)** (Precolos study), aimed at investigating the tolerability and initial safety of BC feeding and Safety Outcomes, revealed that bovine colostrum supplementation was not associated with increased feeding intolerance, gastric residual volume or any apparent clinical adverse effects in the BC group. Regarding time to full enteral feeding, Precolos study showed that, in the 2 included Chinese neonatal units, bovine colostrum fed infants reached full enteral feeding of 120 ml/kg/day earlier than standard formula fed infants (p= 0.097).

For the per-protocol analysis, both the time to full enteral feeding of 120 ml/kg/day and the time to full enteral feeding of 150 ml/kg/day, were significantly shorter for bovine colostrum versus standard formula fed infants (medians 14 and 23 versus 19 and 29 days, respectively, both P<0.05).

Moreover, similar to our results, **Ismail et al. (2021) showed** a reduction in feeding intolerance among the bovine colostrum group cases, where feeding intolerance developed in 1 case (3.1%) in the bovine colostrum group versus 9 cases (18.8%) in the control group and that difference was statistically significant (p=0.03). On the contrary, **Ismail et al. (2021),** failed to show significant statistical differences regarding time to achieve full enteral feeding between both groups (p= 0.38).

Owing to reduced feeding intolerance and shorter time to reaching full enteral feeding that was significantly noticed among bovine colostrum group in our study, that no doubt resulted in less days on total parenteral nutrition among cases of that group, with mean days (11.8), std (6.917) versus mean days (17.07), std (8.946) in the control group which was statistically significant (p<0.001). On the contrary, **Juhl et al. (2018)** (Precolos study), reported that Days on PN did not differ between the 2 groups in any of the countries (neonatal units of China or Denemark). Similarly, **Ismail et al. (2021),** showed no significant differences regarding Days on PN between both groups median (p= 0.83).

In the context of duration of hospitalization, our study revealed significant differences between both groups, where duration of hospitalization (days) had a mean (std), 23.8 (10.996) in bovine colostrum group versus 31.95 (15.483) in the control group, which was highly statistically significant (p=0.001). In Contrast, **Ismail et al., 2021,** showed no significant differences, as length of hospital stay (days), median (IQR), 15 (11.5–

22.5) in the bovine colostrum group versus 14 (10–21) in the control group (p=0.49). Similarly, **Sadeghirad et al. (2018)** reported that the duration of hospitalization did not reveal any significance between the groups (mean difference 1.3 days, 95% CI: −13.7 to 16.3).

In our study we detected no significant difference in mortality between both groups, where 2 cases (3.3%) died in the bovine colostrum group versus 3 cases (5%) in the control group (p=0.648). Similarly, in 2017, a study by **Balachandran et al.** and another by **Li, Y. et al.** showed no difference in mortality between both groups. Additionally, in 2018, two more studies revealed similar results **(Juhl, S. M. et al., 2018 and Sadeghirad, B. et al., 2018).**

On the contrary, use of bovine colostrum was associated with significantly decreased mortality without any recorded deaths in the bovine colostrum group compared to 8 deaths (16.7%) in the control group (p=0.015) in a later study by **Awad et al., 2020.**

Conclusion

The use of bovine colostrum instead of infant formula during the first week of life may reduce the incidence of NEC and LOS in preterm infants. It also reduces the time to achieving full enteral intake, days on parenteral nutrition as well as length of hospital stay.

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