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ORIGINAL ARTICLE

Colostrum protocol evaluation for very low birth weight preterm infants

Evaluación de un protocolo de calostro para prematuros de muy bajo peso de nacimiento

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What do we know about the subject matter of this study?

The administration of oropharyngeal colostrum for the very-low-birth-weight infant has shown immunologic advantages, more adequate oral microbiota, and promotes breastfeeding.

What does this study contribute to what is already known?

In this experience, we show the increase in breastfeeding during hospitalization and at discharge by establishing a protocol for early use of colostrum.

Abstract

Early administration of oral colostrum has been recommended in very-low-birth-weight (VLBW) preterm infant care. **Objective: To** evaluate the clinical effect of early colostrum administration on in-hospital outcome and lactation of VLBW preterm infants compared with historical control in an Intensive Care Unit. **Subjects and Method:** descriptive cohort study with historical control of VLBW preterm infants who did or did not receive early oral colostrum, born 1.6 years before and 1.4 years after this protocol, with information collected from the database of infants under 1500 grams at birth and in the colostrum protocol registry. Children born to HIV+ mothers, with hepatitis, chemotherapy, and those born with malformations incompatible with life were excluded. The main perinatal, morbidity, nutritional, and breastfeeding data at discharge were compared. **Results:** 94 patients were born pre-colostrum and 64 in the protocol period (post-colostrum). The groups were comparable in perinatal history. No difference was observed in infectious, respiratory, or gastrointestinal morbidity, progress in enteral feeding, days of parenteral nutrition, and length of hospital stay. There were significant differences in the percentage breastfeeding at discharge (52 vs. 69%, $p < 0.037$) and in average breast milk volume at discharge (70 vs. 102 ml/k/day, $p < 0.012$) in the post-colostrum group. **Conclusions:** Early colostrum administration to preterm infants was associated with a higher volume of maternal milk at discharge, being a good benefit in VLBW preterm infant care.

Keywords:
Colostrum;
Premature;
Very Low Birth Weight;
Breast Feeding;
Neonatal Care

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Introduction

Breast milk is the milk of choice for the newborn, and in preterm very-low-birth-weight (VLBW) infants it is even more relevant, given its effect in reducing severe preterm pathologies such as necrotizing enterocolitis, severe retinopathy, bronchopulmonary dysplasia, and late sepsis[1,2]. One of the important mechanisms of action of breast milk is its immunological properties. Colostrum presents the highest concentration of immune factors[3]. Since the publication, in 2009, on the immunological advantages that could be obtained with oropharyngeal colostrum intake, the administration of oral colostrum from the mother's own milk, fresh or refrigerated in VLBW infants has been developed[4,5].

Colostrum produces immunostimulation of the oropharyngeal mucosa and colonizes it with the maternal bacterial flora, which has acquired great relevance to attenuating the distortion in the acquisition of one's own intestinal flora that determines cesarean delivery and hospitalization[3,6]. In addition to the potential effects of colostrum administration in the preterm infant, early colostrum extraction contributes to greater success in breast milk production during hospitalization[7].

In our Neonatology Unit, there has been a special focus on breastfeeding and, for more than 35 years, we have been transporting and conserving the mother's own milk. For the last 12 years, we have been stimulating the extraction of milk in the first 24 hours of life of the premature infant, without waiting for the mother to visit her premature infant to indicate the extraction. For 5 years, there has been a donated and pasteurized Milk Bank that has allowed the administration of human milk during the first weeks (4 to 6 weeks according to birth weight) to all VLBW infants and, since mid-2018, the early administration of colostrum was initiated according to an established protocol, similar to those published in the literature[4,5].

The objective of this study was to evaluate the effect of early colostrum administration compared with historical control on the in-hospital evolution and lactation of preterm VLBW infants in an Intensive Care Unit.

Subjects and Method

Descriptive cohort study with historical control, before and after the introduction of the early oral colostrum protocol in VLBW infants.

The colostrum program consisted of colostrum extraction from mothers of preterm infants within a few hours postpartum, together with information and images of their baby. The colostrum collected was administered at 0.2 ml volume to those under weighing 1 kilo and 0.4 ml to those over 1 kilo, drop by drop directly into the mouth, every 3 hours for 3 days. The detail of the protocol is attached as additional material.

All VLBW infants born in the Department were included, excluding those born to HIV+ mothers, those with hepatitis B or C, those undergoing chemotherapy, and those born with malformations incompatible with life.

Data were analyzed for VLBW infants born between January 1, 2017, and August 13, 2018 (pre-colostrum group) and between August 14 and March 4, 2020, discharged before April 10, 2020 (post-colostrum group).

Data were obtained from the VLBW registry from the South American collaborative database Neocosur[8] and the colostrum protocol registry.

The main perinatal data, incidence of morbidity, duration of ventilatory support, age at 100 ml/k/day enteral feeding, days on parenteral nutrition, and volume and proportion breastfed at discharge were compared between both groups.

Late sepsis was defined as the presence of bacteremia, with clinical involvement and laboratory tests compatible with infection. Necrotizing enterocolitis was defined as a picture of intestinal involvement with radiological findings of pneumatosis (Bell's grade II)[9]. Surgical enterocolitis was considered if the diagnosis of intestinal necrosis was confirmed during surgery, without evidence of volvulus or other cause. The Neocosur database showed the number of days of invasive mechanical ventilation, positive airway pressure support, number of days of oxygen supply, duration of hospitalization, weight, and gestational age at discharge. In addition, information was obtained on breastfeeding at 36 weeks or at discharge and the percentage of the total oral volume of breast milk in the previous 2 to 3 days.

There were no changes in feeding practices between 2017 and 2020. Feeding initiation and progression were determined by the treating physician. Feeding was done with their own mother's milk and, if this was insufficient, donated human milk was used until 4 to 6 weeks depending on birth weight.

Descriptive statistics were used. Data are presented as mean and standard deviation in parameters where normal distribution was assumed and as median and interquartile range if Bartlett's test suggested different variances. Differences were analyzed using the ANOVA, Kruskal-Wallis, chi-square, Fisher, and Odds Ratio (OR) tests. A $p < 0.05$ was considered statistically significant. The data were analyzed using Excel and Epiinfo 7.

The study was approved by the Ethics Committee of the South-East Metropolitan Health Service on June 3, 2021.

Results

94 preterm VLBW pre-colostrum infants and 64 post-colostrum infants were included. Table 1 shows the comparative data of the two groups. The groups were similar in birth weight (median 1125 g pre-colostrum group and 1146g post-colostrum group) and gestational age (29 weeks for both groups). A higher number of multiple pregnancies was observed in the post-colostrum period (18.1% vs 31.3%), although the difference was not statistically significant.

Table 2 shows the variables of potential effect. No changes were observed in the incidence of respiratory morbidity, necrotizing enterocolitis, late sepsis, age at reach 100 ml/k/day of enteral feeding, or days of parenteral nutrition. No differences were observed in the duration of hospitalization or the gestational age at discharge for both groups (39.4 weeks and 39.5 weeks).

There was a significant difference in the percentage of breastfeeding at discharge (52% vs. 69%, $p < 0.037$), with the post-colostrum group presenting an OR of 1.98 (95% CI 1.12- 3.56, $p < 0.026$) which was higher compared with the pre-colostrum group. Breast milk volume at discharge was also significantly higher in the post-colostrum group (70 ml/k/day vs 102 ml/k/day, $p < 0.012$) (table 2).

Discussion

In the two periods analyzed, there was an association between implementing a colostrum administration protocol and increased breastfeeding at discharge in preterm VLBW infants.

As has been described in the literature, early milk expression and administration to preterm infants are associated with better breastfeeding adherence during hospitalization[7,10]. This is not the only factor since maternal commitment is required to continue expressing every 3 to 4 hours and transport to the neonatology unit, as well as daily skin-to-skin contact during hospitalization, early breastfeeding, the use of a double pumping system, and the support of lactation counselors to achieve a good volume of milk from the mother for preterm VLBW infants[11-13].

The level of lactation presented in VLBW infants at discharge can be compared with the average data presented in the Vermont Oxford Network in the USA in the white population[14]. Improving breastfeeding rates at discharge is essential for VLBW infants and requires systematic surveillance and breastfeeding support by the entire neonatal team, with staff dedicated to this objective.

The reported effects of early administration of oral colostrum include increased secretory immunoglobulin A (IgA) in saliva[15], decreased proinflammatory state by decreasing interleukins 6 and 8[16], increased absorption of IgA and lactoferrin[17], and different oral microbiota that is maintained at the end of the intervention[18]. Recently, a lower incidence of pneumonia associated with mechanical ventilation has been reported[19].

A 2018 Cochrane systematic review described with 6 studies the achievement of earlier total enteral feeding (within 2.5 days) with colostrum stimulation. They found no effect on presenting morbidity and showed low-grade evidence of increased breastfeeding at discharge[20]. Another systematic review of 9 studies showed faster progression of enteral feeding and shorter duration of hospitalization, but no effect on morbidity[21].

In our study, the two periods analyzed could have

Table 1. History of very low birth weight preterm infants before and after use of the colostrum protocol

Periods	Pre-colostrum Average medium or percentage	SD interquartile range	Post-colostrum Average medium or percentage	SD interquartile range	p
n	94		64		
Birth weight g	1125	259	1146	275	0.66
Gestational Age weeks	29.1	2.6	29	2.5	0.7
Maternal age years	28.1	6.2	28.2	7	0.41
Years of schooling	11.1	1.9	11	1.9	0.73
Primipara %	36.6		50		0.09
Multiple pregnancy %	18.1		31.3		0.06
Male sex %	52		64		0.13

SD standard deviation. Analysis : average SD (anova). % (chi square).

Table 2. Evolution of preterm infants with very low birth weight before and after the use of the colostrum protocol

Periods	Pre-colostrum Average medium or percentage	SD interquartile range	Post-colostrum Average medium or percentage	SD interquartile range	p
Mechanical ventilation days *	9	3-19	8	3-15	0.82
CPAP days *	5.5	3-11	5	3-14	0.44
Late sepsis %	33		33.9		0.90
NEC ≥ grade 2 %	10.6		14.1		0.52
Surgical NEC % **	3.2		1.6		0.46
ICH %	26.9		29.7		0.70
Age of enteral 100ml/k/d days	19.8	14.5	20	15.4	0.93
Parenteral Nutrition days	24.6	18.4	21.7	16.7	0.32
BM at discharge ml/k/day	70	73	102	77	**0.012**
% with BM at discharge	52		69		**0.037**
Hospitalization days	73	34	74	33	0.84
GA at discharge	39,4	3.6	39.5	3.4	0.91
Discharge weight g	2867	734	2988	723	0.31

CPAP: continuous pressure on the airway. NEC: necrotizing enterocolitis, GA gestational age ICH: intracranial hemorraghe. BM: breast milk. SD standard deviation. Analysis : average SD (anova). % (chi square). *medium and intercuartile range (Kruskall Wallis). **%(Fisher test).

many other differences in variables affecting breastfeeding. Some factors that may influence milk production and that we have not analyzed are the mothers' education, the sense of self-efficacy for breastfeeding, the number of skin-to-skin contact with their preterm infant, the degree of smoking, the support of lactation personnel, and the overall attitude of the health care team regarding breastfeeding[22,23]. The beneficiary population of our hospital has not changed in recent years and there have been no other changes that could have a significant influence on the above aspects, until the appearance of the pandemic, which dramatically hindered the visit of the parents. On the other hand, this was a protocol of care and there was no record of intervening variables that could influence it.

The increase in breastfeeding at discharge associated with the early administration of colostrum seems to us to be significant. We did not perform multivariate analysis, but in the second period, we observed more twin pregnancies and more first-time mothers. Both factors could have negatively influenced the volume of breastfeeding at discharge, which supports the probable influence of colostrum administration on it.

Contributing to higher breastfeeding at discharge is a relevant factor as it is associated with better neurocognitive and behavioral evolution of VLBW infants in the medium term[24-26].

We expected that colostrum administration could be associated with a decrease in necrotizing enterocolitis (NEC) and its surgical treatment, however, this was not statistically significant. In this case, the VLBW infant that did not have their mother's milk received pasteurized human milk for 4 to 6 weeks, which already influences reducing the risk of NEC[27]. On the other hand, the presentation of NEC is very variable between periods and associated with various factors[28]. The observable clinical effects of a colostrum protocol also depend on the unit's own levels of complications. Two randomized controlled studies on early colostrum supplementation show a significant effect in a unit with a high incidence of sepsis and NEC, but not in a unit with a low incidence[7,29]. The levels of NEC and sepsis in our unit are within the average observed in the Neocosur network[30].

Although early milk extraction was also performed previously, immediate administration of colostrum was not indicated, and the initiation of enteral feeding varied according to the patient's condition and the treating physician's perception. Once enteral feeding was started, intermittent discontinuation was frequent due to different reasons. We believe that the early administration of colostrum could be an additional incentive for the mother to extract more when she cannot directly care for her child, as happens with VLBW infants.

This protocol is incorporated into the clinical practices of the Service but needs to be maintained over time, through a process of quality improvement, with periodic evaluations and reports[31].

Among the limitations of the study is the sample

size, since the start of the restrictive measures of visits at the beginning of the Covid 19 epidemic, during the year 2020, changed the conditions of access to mothers and milk production. Most published studies on the effect of early colostrum administration have a low number of subjects, but the accumulated information may contribute to a future meta-analysis. It is likely that with a larger sample size, other effects of early colostrum administration on VLBW infants' evolution can be identified.

Conclusion

Early extraction of colostrum is a clinical practice that favors the availability of the mother's own milk during hospitalization and at discharge.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee. The authors state that the information has been obtained anonymously from previous data.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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Protocolo uso precoz de calostro

Objetivos:
- Obtener los potenciales beneficios reportados en la literatura:
  - Menor riesgo de infección
  - Beneficios inmunológicos
  - Menor duración de hospitalización
- Potenciar a la madre en su extracción de leche:
  - Lograr mayores volúmenes
  - Lograr mayor lactancia al alta
- Potenciar a los médicos sobre el inicio precoz de alimentación:
  - Reducir duración de régimen 0
  - Uso precoz de calostro y leche intermedia no congelada
  - Lograr aporte enteral total o 100 ml/k más precoz

Criterios de inclusión:
- Todo RN menor o igual de 1.500 g
- Gemelos donde uno sea menor o igual a 1500 g, se ingresaran a los dos RN independiente que el otro gemelo sea mayor de 1.500 g

Criterios de exclusión:
- Hijo madre VIH (+)
- Hijo madre con Hepatitis B o C
- Hijo madre en tratamiento con Quimioterapia
- RN con malformación incompatible con la vida (ejemplo Síndrome de Potter)

Volumen de administración de calostro
- Dosis de 0,4 ml oral a los RN mayor de 1.000 g
- Dosis de 0,2 ml oral a RN menor de 1.000 g

Frecuencia de Administración
- RN en régimen 0 administración cada 3 h
- RN con aporte enteral cada 3 h. Administración cada 3 h
- RN con aporte enteral cada 4 h. Administración cada 4 h

Duración Protocolo

La Duración del protocolo está determinado por el número de dosis de calostro que son 24. Todo Rn debe completar 24 dosis independiente de los días de vida

Materiales
- Jeringas de Tuberculina
- Riñonera
- Guantes de procedimiento
- Equipo de extracción de leche (Set de leche, extractor eléctrico)
- Registros de extracción precoz
- Equipo de protección (Gorro, mascarilla y guantes)
- Refrigerador
- Unidad refrigerante
- Unidad aislante (bolso)
- Alcohol 70°
- Lápiz, plumones y etiqueta autoadhesiva.
- Equipo de protección de fluidos corporales : gorro, mascarilla, delantal y guantes de procedimiento
- Planilla Control de ingreso de calostro
- Planilla de control de temperatura
- Planilla de registro de extracción precoz
- Autorización de captura de imagen del procedimiento

1. Procedimiento de Extracción de calostro

1. Informar a personal a cargo de la sala donde se encuentre la madre (recuperación, UCI, UTI, etc.).
2. Informar a la madre sobre el objetivo de la estimulación y/o extracción precoz de calostro
3. Realizar lavado de manos
4. Facilitar una postura cómoda según tolerancia para realizar extracción
5. Realizar masaje de forma circular en la mama, para estimular reflejo eyecto lácteo
6. Estimular con bomba eléctrica 15 minutos por mama áprox. (según tolerancia).
7. En caso de extraer calostro rotular mamadera con apellidos del RN, fecha, hora y sala.
8. Trasladar calostro obtenido a sala de protocolo para ser porcionado.
9. Informar a matrona a cargo del paciente
10. **Iniciar extracción precoz dentro de las 3 primeras horas postparto y repetir procedimiento cada 3 h** hasta que la madre se pueda trasladar al lactario por sus propios medios.
11. Registrar en hoja correspondiente fecha y hora de estimulación o extracción, y ml de calostro obtenidos (si no se obtiene calostro igual se debe registrar) (hoja anexo1)

Consideraciones

- ✓ Al momento de realizar la extracción del calostro informar a la madre de manera general el estado y evolución su hijo (apoyarse con Fotos y videos).

2. Traslado de Calostro a sala de Protocolo Calostro (sala de Proyectos)

El transporte se hará en una unidad aislante (bolso exclusivo para calostro) y unidades refrigerantes ambos desinfectadas previamente con alcohol 70 ° permitiendo mantener la temperatura interior a un máximo de 5° C.

3. Fraccionamiento del Calostro

1. La Matrona a cargo del fraccionamiento debe usar equipo de protección de fluidos corporales: se coloca gorro y mascarilla, a continuación debe realiza lavado clínico de manos y postura de guantes de procedimiento.
2. Porcionar 0,2 o 0,4 ml de calostro según corresponda en jeringas de 1 ml (tuberculina), optimizando la distribución para evitar pérdidas de calostro.
3. Tener presente que de la **PRIMERA EXTRACCIÓN SOLO** dosificar 16 jeringas, ya que el calostro **solo dura 48 h refrigerado.**
4. Rotular cada jeringa con etiquetas autoadhesivas y con marcador indeleble los siguientes datos :
   a. Apellidos Rn
   b. Fecha
   c. Hora
5. Rotule cada riñonera con nombre del RN y con marcador rojo fecha de vencimiento del calostro

4. Almacenamiento del Calostro

1. Designar una repisa del refrigerador por paciente, en caso de gemelos se utiliza una sola repisa para ambos.
2. Distribuir riñoneras en repisa por norma FIFO (lo primero que entra es lo primero que sale. Riñoneras con calostro más antiguo se colocan adelante).
3. Mantener temperatura del refrigerador entre 0-10° C
4. Registrar temperatura del refrigerador en hoja de curva cada 12 h
5. El **calostro solo dura 48 h**. Por lo que calostro obtenido que no sea administrado dentro de este tiempo enviar a SEDILE para congelar.
6. Registre en hoja de enfermería administración del calostro destacándolo y enumerando la dosis administrada.

Consideraciones:

- ✓ La temperatura debe permanecer entre 0° C y 10 °C, si esta fuera del rango no administrar calostro
- ✓ El calostro permanecerá como máximo 48 horas refrigerado, pasado ese periodo se eliminará.
- ✓ Administrar Calostro según fecha de expiración, utilizando sistema FIFO (primero en entrar, primero en salir)

5. Administración

La administración de calostro estará a cargo de la matrona a cargo del RN (paciente en Ventilación y Cpap) o técnico paramédico (otros pacientes).

Resguardar de un ambiente protegido y tranquilo para la administración del calostro.

1. Temperar calostro en incubadora del paciente hasta lograr temperatura ambiente.
2. Paciente tranquilo, bien posicionado en su nido de contención.
3. Realizar aspiración Oro faríngea y/o Endotraqueal (solo si esta última corresponde), previo a administración del calostro.
4. Se iniciará el reconocimiento olfatorio, acercando la jeringa a su nariz (mínimo 5 segundos)
5. Administrar 1 gota por lado de la comisura de la boca, dando pausas de 5 segundos entre gota y gota (se debe evitar que el calostro sea expulsado bruscamente)
6. Registrar la existencia de alguna alteración y variación de los parámetros fisiológicos durante la administración de calostro
7. Una vez finalizado el procedimiento contener al niño y promover la vuelta a la calma.
8. Registrar el procedimiento en hoja de enfermería destacándolo y enumerando la dosis administrada en orden consecutivo.
9. Son **24 dosis de calostro en total para completar protocolo**, independiente del tiempo de vida del RN (estudios han mostrado que la producción de calostro se puede extender hasta 7 días en madres de RN prematuros)

Consideración

- ✓ La administración de calostro es independiente de la gravedad del paciente, en relación a drogas vaso activas, uso de indometacina, tipo de soporte ventilatorio.
- ✓ En caso de enterocolitis precoz confirmada (no sospecha) la administración dependerá del médico tratante.

Hojas de Registros

1. Control de Temperatura Refrigerador
2. Control de Ingreso de calostro y Registro Extracción precoz
3. Ficha RN Protocolo Calostro
4. Autorización de captura de imagen del procedimiento

Matronas a cargo de extracción de Calostro

1. Lunes a Viernes 8:30-17:30 Matrona de Lactancia y Técnico paramédico lactario
2. Lunes a Viernes 17:30-20:30 Matrona de clínica o Matrona Uciprem
3. Sábado-Domingo y Festivos, en el día Matrona de Clínica y Técnico Paramédico Lactario
4. Turnos de noche Matrona de Uciprem.

Matrona a cargo de Administración

- Matrona a cargo del paciente

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