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ORIGINAL ARTICLE

Exclusive breastfeeding and disease evolution in hospitalized infants with bronchiolitis

Lactancia materna exclusiva y evolución de la enfermedad en lactantes hospitalizados por bronquiolitis

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

The lack of breastfeeding is a risk factor for developing severe respiratory infections. The effect of breastfeeding on patients hospitalized due to bronchiolitis is not well understood.

What does this study contribute to what is already known?

In this prospective cohort study, we studied the effect of breastfeeding on the outcome of patients hospitalized due to bronchiolitis. Breastfeeding was a protective factor for days of oxygen therapy and days of hospitalization.

Abstract

Bronchiolitis is the main reason for hospitalization in infancy. Breastfeeding is a protective factor against infections, however, although there is evidence that breastfeeding could prevent hospitalizations due to bronchiolitis, its effect in patients already hospitalized because of this disease is less clear. **Objective:** To evaluate if there are differences in the evolution of patients hospitalized due to bronchiolitis fed with exclusive breastfeeding (EBF) vs. breast milk substitutes (BMS). **Patients and Method:** Prospective cohort study. Children hospitalized due to bronchiolitis aged from 1 to 6 months were included. Evolution was compared with respect to days of hospitalization, days of oxygen therapy, requirement of high-flow nasal cannula (HFNC), presence of associated pneumonia, transfer to intensive care, and death. **Results:** During the study period, 131 infants hospitalized due to bronchiolitis met the selection criteria, 54 were fed with EBF, 29 with BMS, and 48 received mixed feeding. The EBF group required significantly fewer days of oxygen therapy (5.1 ± 2.4 *vs.* 6.6 ± 3.5; $p < 0.02$) and hospitalization (7.0 ± 2.4 *vs.* 8.4 ± 3.6; $p < 0.04$) than the BMS group. Although males in the BMS group required on average more days of hospitalization and oxygen therapy, this difference was not statistically significant. No deaths were recorded in the groups studied. **Conclusion:** Patients fed with EBF required fewer days of oxygen therapy and hospitalization than those who received BMS.

Keywords:
Bronchiolitis;
Human Milk;
Breastfeeding;
Oxygen Therapy;
Length of Stay

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Introduction

Bronchiolitis is a very common acute respiratory infection in childhood mainly caused by the respiratory syncytial virus (RSV)[1]. During the first two years of life, almost 100% of children develop some degree of RSV infection, but only 1% require hospitalization[2]. However, in patients with risk factors, the need for hospitalization may be higher. Prematurity, male sex, underlying chronic conditions, low socioeconomic status, tobacco smoke exposure, and lack of breastfeeding are risk factors associated with a higher rate of hospitalization[3].

Breastfeeding is universally accepted as a protective factor against different types of infections[4,5]. Moreover, the lack of breastfeeding is a risk factor for developing severe respiratory infections requiring hospitalization[6] but the effect of breastfeeding on the evolution of hospitalized patients is less clear.

The benefit that breastfeeding has on bronchiolitis would present differences according to the sex of the patient, favoring females more than males with RSV infection[7]. However, the sex differential effect that breastfeeding could have, to our knowledge, has not been evaluated in patients hospitalized due to bronchiolitis.

The objective of this study was to evaluate differences in the evolution of patients hospitalized due to bronchiolitis fed with exclusive breastfeeding (EBF) compared with those receiving breast milk substitutes (BMS).

Patients and Method

Prospective cohort study that included patients aged 1 to 6 months, hospitalized due to bronchiolitis in a tertiary pediatric hospital, between October 1, 2018, and October 31, 2019. Bronchiolitis was defined as the first or second episode of wheezing associated with clinical manifestations of viral infection in children under 2 years of age[1]. We excluded those receiving mixed feeding, with chronic lung disease, heart disease, undernutrition, prematurity (as a whole), or those who had developed bronchiolitis as an intercurrent during hospitalization.

Exposure variables were the type of feeding and the patient's sex.

Outcomes included days of hospitalization, days of oxygen therapy, requirement of high-flow nasal cannula (HFNC), presence of associated pneumonia, transfer to intensive care, and death. All clinical decisions on outcome variables were made by the treating team without intervention by the investigators.

In addition, other variables were recorded to better categorize the population, including age, tobacco smoke exposure (when at least one member of the household is a smoker), overcrowding (when there are more than three people per room in the patient's home), atopic history (personal or first-degree family history of rhinitis, atopic dermatitis, or asthma), incomplete vaccination, and respiratory syncytial virus infection.

To compare, study groups were defined according to their type of feeding at the time of admission as follows:

Exclusive breastfeeding (EBF)

Patients fed with exclusive breast milk according to WHO definition[8]. Infants receiving only breast milk (including expressed or wet nurse's milk) during the first 6 months of life, and no other food or drink, not even water, except oral rehydration salts, drops, and syrups (vitamins, minerals, and medicines).

Breast milk substitutes (BMS)

Patients fed only with breast milk substitutes from birth[8], considering as substitutes any milk product (or product that can be used as a substitute for milk) that is specifically marketed for this purpose.

Statistical analysis

Continuous variables were described using mean with standard deviation or median with interquartile range (IQR) according to whether they adjust to normality (Kolmogorov-Smirnov test). Categorical variables were described using relative and absolute frequencies. Quantitative variables were compared by t-test for independent samples or Mann-Whitney U test according to whether they adjusted to normality. Proportions were compared by Fisher's exact test. Multiple linear regression analysis was performed to evaluate the effect of the exposure variable and was also used to evaluate the covariates on the outcome variables that had statistically significant differences in the bivariate analysis. Two-way ANOVA was used to evaluate the differential effect of feeding type according to the patient's sex. In all cases, a p-value < 0.05 was considered statistically significant.

Ethical considerations

Informed consent was requested and obtained from the legal guardian of each patient. The study was authorized by the Research Ethics Committee of the institution. The project was incorporated into the public research registry of the City of Buenos Aires (No. 144/18).

Results

In the study period, 131 children aged 1 to 6

months hospitalized due to bronchiolitis met the selection criteria: 54 were fed with EBF, 29 with BMS, and 48 received mixed feeding. Patients in the EBF and BMS groups were included in the study (n = 83). The median age was 3.3 months (IQR 2.4-5.3), 36.1% were female, 38.6% had incomplete vaccinations, 31.3% lived in overcrowded conditions, 48.2% were exposed to tobacco smoke, and RSV was identified in 37.4%. All patients required oxygen therapy on admission. The overall mean days of oxygen therapy was 5.6 ± 2.9 and hospitalization was 7.5 ± 3.0.

First, we analyzed the characteristics of both groups. A similar distribution of the exposure variables and covariables was observed in both groups (Table 1).

Regarding the outcomes studied, days of oxygen therapy (p = 0.024) and days of hospitalization (p = 0.044) presented significant differences according to the type of feeding in the bivariate analysis. The need for HFNC and the frequency of pneumonia were similar in both groups. Only 2 patients required transfer to the intensive care unit, with no statistically significant difference (both cases were males in the BMS group). No deaths were recorded in the groups studied (Table 2).

Second, using a multiple linear regression model, the effect of the outcome variables and covariables on days of oxygen therapy and hospitalization was analyzed. For days of oxygen therapy, only the effect of type of feeding (EBF; p = 0.019) was significant, while for days of hospitalization, the effect of type of feeding (EBF; p = 0.024) and overcrowding (p = 0.002) was significant (Table 3).

Finally, using the two-way ANOVA, the interaction of the effect that feeding type and sex could have on oxygen therapy days and hospitalization days was evaluated. The interaction between type of feeding and sex was not statistically significant regarding oxygen therapy days (F 0.91, p 0.344) or hospitalization days (F 1.85, p 0.177). Table 4 describes days of oxygen therapy and hospitalization according to sex and type of feeding.

Discussion

In this study, children hospitalized due to bronchiolitis fed with EBF required fewer days of hospitalization and fewer days of oxygen therapy than those fed exclusively with BMS. These results are consistent with those presented in other previously published work. In a prospective study, Dornelles et al.[9] evaluated the relationship between the duration of EBF and days of hospitalization and oxygen therapy in infants aged 0 to 6 months diagnosed with bronchiolitis, observing that the duration of EBF was inversely related to the duration of hospitalization and days of oxygen therapy. Specifically, for each month of EBF, there was a reduction of 11 h in oxygen requirement in hospitalized patients. Another prospective observational study conducted in India explored the relationship between EBF and days of hospitalization due to bronchiolitis showing similar results. Exclusively breastfed infants remained hospitalized for less than seven days, while those fed with mixed feeding or BMS alone required hospitalization for more than seven days[10]. In contrast to these studies, Vereen et al. found no difference in the hospitalization time of patients with bronchiolitis according to their feeding type[11]. However, in such work, patients who had ever been breastfed were compared with those who had never been breastfed. This difference in the definition of exposure, with respect to that used in our study, could explain the difference in the results. Studies on the effect of breast milk on respiratory pathologies available in the literature have varied definitions of exposure, which makes direct comparisons between studies difficult[12].

Although in our series the average number of days of hospitalization (7.5 d) is above that usually report-

Table 1. Study groups characteristics

	EBF (n=54)	BMS (n=29)	p
Age in months	3.0 (2.3-5.2)	3.7 (2.9-5.3)	0.201*
Female sex	42.6% (23)	24.1% (7)	0.075**
Incomplete vaccinations	38.9% (21)	37.9% (11)	0.562**
Atopia	40.7% (22)	41.4% (12)	0.569**
Overcrowding	33.3% (18)	27.6% (8)	0.389**
Tobacco smoke exposure	50.0% (27)	44.8% (13)	0.414**
RSV	38.9% (21)	34.5% (10)	0.440**

Categorical variables are described using relative and absolute frequencies. Continuous variables are described using median with interquartile range according to the observed distribution. EBF: Exclusive breastfeeding. BMS: Breast milk substitutes. RSV: Respiratory Sintitial Virus. *Mann Whitney U test. **Fisher´s exact test.

Table 2. Outcome variables by study group

	EBF (n=54)	BMS (n=29)	p
HFNC	16.7% (9)	24.1% (7)	0.294**
Pneumonia	33.3% (18)	20.7% (6)	0.170**
Transfer to PICU	0.0% (0)	6.9% (2)	0.119**
Death	-	-	-
Days of oxygen therapy	5.1 (2.4)	6.6 (3.5)	0.024***
Days of hospitalization	7.0 (2.5)	8.4 (3.6)	0.044***

Categorical variables are described using relative and absolute frequencies. Continuous variables are described using median with interquartile range according to the observed distribution. EBF: Exclusive breastfeeding. BMS: Breast milk substitutes. HFNC: High-flow nasal cannula. PICU: Pediatric Intensive Care Unit. **Fisher´s exact test. ***t-test for independent samples.

Table 3. Multiple linear regression analysis

	Beta Coefficient (IC 95%)	p
*Days of oxygen therapy**		
EBF	-1.58 (-2.89 a -0.27)	0.019
Age in months	-0.17 (-0.59 a 0.25)	0.417
Female sex	-0.52 (-1.81 a 0.77)	0.423
Incomplete Vacination	-0.36 (-1.66 a 0.94)	0.584
Atopia	0.96 (-0.31 a 2.22)	0.137
Overcrowding	1.34 (-0.04 a 2.72)	0.057
Tobacco smoke exposure	-0.42 (-1.70 a 0.86)	0.515
RSV	1.11 (-0.18 a 2.39)	0.091
*Days of hospitalization**		
EBF	-1.49 (-2.78 a -0.20)	0.024
Age in months	-0.25 (-0.65 a o.16)	0.234
Female Sex	-0.74 (-2.01 a 0.53)	0.248
Incomplete vaccination	0.25 (-1.03 a 1.53)	0.694
Atopia	0.76 (-0.48 a 2.01)	0.227
Overcrowding	2.15 (0.79 a 3.51)	0.002
Tobacco smoke exposure	-0.38 (-1.65 a 0.88)	0.546
RSV	1.16 (-0.10 a 2.43)	0.071

EBF: Exclusive breastfeeding. BMS: Breast milk substitutes. RSV: Respiratory Sintitial Virus. *R-square: 0.19, ** R-square: 0.24.

Table 4. Effect of feeding type and sex on oxygen therapy days and hospitalization days was evaluated

		Days of oxygen therapy	Days of hospitalization
Female with EBF	(n = 23)	5.0 (2.3)	6.9 (2.4)
Female with BMS	(n = 7)	5.4 (1.8)	6.7 (1.7)
Male with EBF	(n = 31)	5.1 (2.5)	7.1 (2.5)
Male with BMS	(n = 22)	7.0 (3.9)	9.0 (3.9)

Variables are depicted with mean and standard deviation. EBF: Exclusive breastfeeding. BMS: Breast milk substitutes.

ed in other centers, particularly in the northern hemisphere[11], it is consistent with previous findings in our region[13] and is most likely the result of many complex factors, including socioeconomic characteristics of the patients and institutional culture, whose analysis is beyond the scope of this study.

The effect of breast milk is not limited to the evolution during hospitalization. Breastfed infants have a lower incidence of respiratory infections, shorter duration of episodes[14], and a lower hospitalization rate due to this reason[15]. In a meta-analysis covering 9 studies in industrialized countries, it is estimated that 26 women feeding their infants with EBF would avoid at least one hospitalization due to lower respiratory pathology since EBF in the first 4 months of life reduces by one third the risk of hospitalization due to respiratory causes[6].

Several physiological factors could explain the effects of breast milk observed in this study. First, breast milk has an effect on respiratory physiology where breastfed infants present better lung development resulting in a higher forced vital capacity[16]. In a study of infants hospitalized due to bronchiolitis, the duration of breastfeeding had an inverse relationship with the development of an obstructive respiratory pattern[17].

Secondly, breast milk conditions the development of the nasopharyngeal microbiome. Biesbroek et al. found that breastfeeding during the first month of life is associated with a specific nasopharyngeal microbiota profile at 1.5 months of age, which is more stable, and with a lower incidence of respiratory infections during the first two years of life[18].

Third, breastfeeding has broad effects on immunity. A variety of molecules present in breast milk provide passive immunity against respiratory infections such as IgA[19], IgG[20], and lactoferrin[21]. In addition, the immunomodulators present in breast milk favor a Th1-type immune response[22].

It is important to note that the composition of breast milk is variable. Milk from mothers of RSV-in-

fected infants has a higher cell count and a specific cytokine profile[23]. This fact highlights the existing communication between mothers and infants through breast milk. Accordingly, breast milk could have an epigenetic effect that would explain the protection against transmissible and non-transmissible diseases in childhood and adulthood[24].

Additionally, the protective and preventive function of breast milk is present in other non-respiratory infectious diseases. In the case of diarrhea, breastfed infants had a lower incidence of diarrhea, lower hospitalizations, and lower mortality rates[25]. Similar results were observed in patients with bronchopneumonia, meningitis, or sepsis[10].

As strengths of our study, we highlight the design chosen with prospective data collection, which allowed us to avoid biases typical of retrospective studies and to have study groups with similar distribution of potentially confounding variables. To avoid selection bias, the criteria for hospitalization, oxygen requirement assessment, and hospital discharge were decided by the treating team, according to the regulations of the institution, with no influence from the investigators. Finally, the main strength of this study is the conformation of the study groups. By comparing the evolution of children exclusively breastfed in relation to those fed with BMS only, the inaccuracy of the heterogeneous effect that breast milk could have on mixed feeding was avoided.

Finally, the main limitation of this study is the sample size. Our sample was sufficient to meet the main objective. However, a larger sample might have allowed us to demonstrate the significant differences observed between males and females in relation to days of hospitalization and oxygen therapy, as has already been postulated[7]. Unfortunately, the development of the COVID-19 pandemic made it impossible to continue with the study, due to the absence of hospitalizations due to bronchiolitis in the following winter[26].

Conclusion

Exclusively breastfed patients required fewer days of oxygen therapy and fewer days of hospitalization than those who were fed only with breast milk substitutes.

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: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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