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Brief Report

Human Milk Feeding for Septic Newborn Infants Might Minimize Their Exposure to Ventilation Therapy

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ABSTRACT

Background. It is well established that human milk feeding contributes in limiting lung disease among vulnerable neonates. The primary aim of this research was to compare the need for mechanical ventilation of human milk-fed sick neonates with that of formula-fed sick neonates. Methods. All late preterm and full term infants from a single center with findings of sepsis, from 2002 to 2017, were identified. Data regarding infant feeding during hospital admission were recorded. Multivariate logistic regression analyses were performed to assess the impact of the type of milk on ventilation support and main neonatal morbidities. Results. The total number of participants was 322 (human milk group = 260, exclusive formula group = 62). On bivariate analysis, 72% of human milk-fed neonates did not need oxygen therapy nor respiratory support versus 55% of their formula-fed counterparts (P<0.0001). Accordingly, invasive mechanical ventilation was

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required by 9.2% of human milk-fed infants versus 32% of their formula-fed counterparts (P=0.0085). These results hold true in multivariate analysis, indeed human milk-fed neonates were more likely to require less respiratory support (OR=0.44; 95% CI: 0.22, 0.89) when compared to those who were exclusively formula-fed. Conclusion. Human milk feeding might minimize exposure to mechanical ventilation.

Keywords: human milk; oxidative stress; oxygen therapy; premature infant; sepsis; newborn infant; ventilation support

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INTRODUCTION

Human milk (HM) consists of a spectacular array of biologically active components to facilitate optimum development and boost immunity of newborn infants. Studies are currently underway to evaluate the role of most of these molecular and cellular elements. According to these studies, antioxidants in human milk appear to play a pivotal role in prevention of lung injury. Around birth, a delicate balance exists between the production of reactive oxygen species (ROS) and their detoxification through various biological systems [1]. At moderate concentrations, free radicals play several beneficial roles in achieving healthy fetal or neonatal development. However, the balance may be disturbed due to increased generation of ROS or inadequate detoxification, both of which are oxidative malfunctions inherent to many conditions affecting newborn infants, notably preterm birth, hyperoxia or inflammation [2].

HM conveys a considerable amount of antioxidant molecules [3]; antioxidants from HM can remove ROS directly, change the activity of antioxidant enzymes,

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or regulate signaling pathways to achieve their antioxidant actions [4]. Hence, newborn infants are heavily dependent on HM to counterbalance the oxidative stress that characterizes different stages of the perinatal period. During labour, the neonate is subject to a hyperoxic challenge [5]. There is a five-fold increase of oxygen tension, from the intrauterine hypoxic environment to the extrauterine normoxic environment. After birth, sick neonates or preterm infants have reduced antioxidant defenses. Regarding neonatal sepsis, pathogenic invasion represents the initiation of sepsis, but the sepsis syndrome is subsequently maintained by a cascade of oxidative mechanisms and a marked disruption of the antioxidant metabolic pathways [6] which, once activated, act independently from the pathogens themselves. On the other hand, since premature birth interrupts antioxidant defense mechanisms that mature during late gestation, preterm infants are also highly sensitive to oxidative stress [7].

Oxidative insult is a salient part of lung injury that begins as acute inflammation in respiratory distress disease and can then evolve into chronic and structural scarring. Hyperoxia directly causes alveolar epithelium apoptosis, and this in turn leads to aberrant airway healing and remodeling [4]. While there are conflicting findings in the area of neonatal respiratory support, it is generally accepted that previous lung inflammation makes the lung endothelium and epithelium more susceptible to oxidant-induced injury during mechanical ventilation [8].

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Given that HM possesses a much stronger antioxidant potential than bovine infant formulas [9] and the reported antioxidant depletion among preterm or septic neonates, the aim of this study is to analyze the impact of HM feeding on lung protection or type of mechanical ventilation in critically ill neonates.

METHODS

Study population, design, location, and period.

This analysis was conducted using data from a retrospective study conducted on neonates with a diagnosis of sepsis. Detailed description of the study design and methods is published [10]. In brief, this is a secondary analysis of a review of the electronic medical records of newborn infants from the neonatal intensive care unit (NICU) of Sant Pau Hospital, which is a tertiary referral unit for the province of Barceloma, Spain. The unit consists of 10 intensive care and 7 high-care beds, with approximately 350 admissions per year and a bed occupancy rate of 90%.

A cohort study was undertaken where all late preterm infants and full term infants up to 28 days of age, with clinical and laboratory findings of bacterial or viral sepsis between January 2002 and December 2017 were identified. The computerized system of the Neonatal Unit provided the retrospective data, which included maternal parity and gravida, maternal diseases, infants' demographic and perinatal characteristics, feeding type, and early clinical features.

Data regarding infant feeding during hospital stay were recorded as human milk, formula, or combined feeding. For the purpose of the study, we determined the following definitions for neonatal feeding: "human milk" when any human feedings (mother's own milk +- donor milk) were administered or "exclusively

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formula" when feeding included all meals of this type.

Primary outcome

The primary outcome of this analysis was mode of respiratory support and oxygen supplementation among late preterm or full term newborn infants with a history of sepsis. Our aim was to observe whether exclusive formula feeding helped predict respiratory support practices. Infant feeding type was an independent variable and respiratory support was the dependent variable in this initial analysis.

Secondary outcomes

The secondary outcomes were neonatal characteristics, morbidities or procedures according to feeding type. They included: fetal status at birth, acidosis, hypotension, abnormal neurological examination, abnormal brain scan, meningitis, positive blood cultures, CPAP and/or oxygen administration, ventilation type, discharge weight and days of hospital stay.

Analysis plan

We used descriptive statistics to produce counts and percentages regarding type of feeding of newborn infants with a history of neonatal sepsis in the registry. The primary and secondary outcomes, infant and maternal characteristics were compared using Fisher's Exact, χ^2 ot *t* tests depending on variable type; P-values were obtained from bivariate comparisons as a function of each individual risk factor.

Multivariate logistic regression analyses were performed to assess the impact of the type of milk on primary outcome, and to find out the independent contribution of each factor towards neonatal outcome. Based on statistical significance in bivariate comparisons, factors which were highly predictive of the primary outcome were included in a model to

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adjust for potential confounding risks. These covariates were removed from the multivariate logistic regression model via backward selection if they no longer had significance when added to the model. Heart failure and respiratory failure were not included in the adjusted model because of collinearity with respiratory support. No methods were used to adjust for any potential bias.

The SPSS software version 21.0 (SPSS Chicago, Illinois, USA) was used for statistical analysis and data management.

Ethical considerations

This study received approval from the Santa Creu i Sant Pau University Hospital Clinical Studies Ethics Committee on December 20, 2020 with decision number: IIBSP-ENT-2020-152. Since the study was conducted retrospectively, spanning over a period of two decades, and the data were extracted from patient files, no informed consents were obtained.

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RESULTS

A total of 25,152 infants were born alive at our delivery unit between 2002 and 2017, and 4,210 (16.7%) of them were admitted to our NICU during the study period. Finally, 322 (7.6%) admitted neonates matched the study inclusion/exclusion criteria for participation in the final analysis. In Table 1 we report the patients' baseline demographics for the two feeding-type groups: neonates who received any amount of HM and neonates who received only formula (EF). We found no differences for maternal-perinatal morbidity, gestational age, sex, 5-minutes Apgar score, length or head circumference at birth. EF infants were more likely to have been delivered by C-section, and had lower birth weight and lower 1-minute Apgar score than HM infants. However, these relationships did not persist when introduced in the multivariate model.

Table 2 compares short-term neonatal outcomes according to feeding type. On bivariate analysis, EF infants required higher respiratory support and higher Fraction of inspired Oxygen (FiO_2) levels than HM infants (0.28 versus 0.39, P=0.0001). In addition, 72% of HM-fed neonates did not need oxygen therapy nor respiratory support versus 55% of their EF-fed counterparts (P<0.0001). Accordingly, invasive mechanical ventilation was required by 9.2% of HM-fed infants versus 32% of their EF-fed counterparts (P=0.0085). Other neonatal short-term outcomes did not differ between the two groups.

In the adjusted multivariate logistic regression model (Table 3), HM-fed newborn

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infants were more likely to require less respiratory support (OR=0.44; 95% CI: 0.22, 0.89) when compared to those who were exclusively formula-fed (than EF-fed newborn infants?). Gestational age, altered alertness state, altered muscle tone, sepsis score, meningitis or abnormal brain scan were covariates that remained significant in the final model. Important confounders in the adjusted model were gestational age and meningitis as they were associated with feeding type (P=0.056 and P=0.084, respectively) and type of respiratory support. However, even when controlling for these covariates, HM-fed newborns had 55% (adjusted OR, 0.449) lower odds of receiving invasive respiratory support than EF-fed newborns.

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DISCUSSION

This study demonstrates that EF-fed septic late preterm or full term newborn infants require higher respiratory support than their HM-fed counterparts. More than one hundred studies have analyzed the preventing role of HM feeding on bronchopulmonary dysplasia [11]. However, as far as we are aware, no more than five papers in the last twenty years have addressed the link between HM feeding and lower ventilation requirements of critically ill neonates.

In 2005, Schanler et al. [12] reported that the mean duration of mechanical ventilation of 92 extremely preterm formula-fed neonates was 19 days in contrast with 12 days for their 70 counterparts fed on mother's own milk (P=0.03). Ten years later, a paper related to the implementation of a donor milk policy in a NICU reported that the number of days on supplemental oxygen therapy decreased to the same degree as the proportion of diet as HM increased within a group of 150 very-low-birth-weight infants [13]. Over the last seven years, three studies have confirmed that increasing the amount of HM helps to improve short term respiratory support outcomes. In 2015, our own multicenter pre–post retrospective study, before and after implementing a donor human milk policy, found that time in oxygen and duration of mechanical ventilation were significantly higher among EF-fed than among HM-fed infants [14]. Hair et al. [15] found a significant reduction of ventilator days among newborn infants with a birth weight <1,250 g on a new feeding protocol of mother's own milk fortified with HM-derived fortifier with respect to their counterparts who received a diet

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of mother's own milk fortified with bovine fortifier and/or preterm formula. Very recently, Sun et al. [16] conducted a prospective cohort study including infants born at <30 weeks' gestation in which mothers of 98 neonates of the intervention group were asked to provide at least one feed per day of fresh HM within 4 hours of milk expression, and the control group included 109 mothers who did not agree to provide fresh HM, but agreed for their infants to receive donor milk or frozen mother's own milk. They found that the fresh HM group had a shorter duration of mechanical ventilation than the control group. Finally, a 2022 meta-analysis shows that not only HM feeding, but also oral care of preterm infants with mother's milk shortens the mechanical ventilation time [17]. It is remarkable that despite large differences in the way the various research groups provide HM to infants in neonatal care, HM is associated in all cases with a reduction of respiratory support. Moreover, our results on need for mechanical ventilation are in line with previous research despite having focused on late preterm or full term neonates unlike the cases described above. As a result, it remains unclear what the optimal dose, type and duration of HM is and which populations of sick neonates or preterm infants might benefit most from HM supplementation to minimize exposure to mechanical ventilation.

HM is a bioactive factory with stem cells, microbiota, growth factors, numerous antioxidants, and immune-boosting properties [18] whose protective role against acute lung disease in infants is well established [19,20], but the mechanism of this beneficial effect is unclear. Several potential explanations can be advanced to

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clarify why we report an increased susceptibility to severe acute lung disease in EF-fed infants compared with those who were HM-fed. In particular, antioxidants are among the most outstanding compounds found in HM [21-23], especially when the target population comprises a group of infected neonates who register a significant elevation of ROS. In this case, the risk for oxidative injury may persist and even increase throughout a sick neonate's hospital course, making antioxidant components of HM beyond the first days of life potentially beneficial. Further, the imbalance of the redox status favoring oxidative pathway activation during sepsis [24] is also a critical factor in the pathophysiology of neonatal respiratory distress [25]. This hypothesis assumes that since HM is a better scavenger of ROS than formula [26], it may defend a large population of neonates with increased oxidative stress, a critical factor that exacerbates perinatal morbidities. However, many other HM biofactors are in play and thus contribute to neonatal lung protection. Notably, observations on oral care with mother's milk in recent years suggest that HM can form a protective layer of the respiratory wall, and play a first-line defense role by reducing oropharyngeal pathogens in ventilated neonates. Alternatively, HM protection against acute respiratory disease may be conferred by passive transfer of humoral immunity, or of any soluble molecule with anti-infective properties [27]. Finally, there is still much to be learned about the immune-modulating role of the microbiota, or the expanding field of HM stem cells.

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Limitations

The large number of included septic infants, and the exclusion of recall bias concerning HM feeding are strengths of our study. We were able to show some variation in mechanical ventilation duration between HM-fed and EF-fed newborn infants. While these findings are important in broadening our knowledge, they are not without limitations.

The sample was taken from the NICU of one hospital over a long period of time, thus further study is needed to determine whether these results generalize to other settings. Feeding type was not the focus of the primary study. Consequently, the questions concerning HM feeding were less detailed than those that would be used in a prospective study. An additional limitation of this study is the use of maternal HM feedings at any time during Hospital admission to represent provision of HM. We were also unable to quantify the volume of HM received, nor distinguish between fresh mother's milk or processed human milk. There are inherent limitations to our retrospective review design, including missing data and lack of standardization of measurement methods. Although the independent association between any HM feeding and less need of mechanical ventilation in septic neonates is supported by our findings, conclusions about causality cannot be established due to the observational design of the study.

CONCLUSION

This study shows that any EF feeding is independently associated with higher respiratory support not only among very pretem neonates, but also among late preterm or full term sick neonates. These results reinforce the theory of HM as a postnatal intervention able to

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mitigate metabolic and immune-related risk factors of respiratory pathologies, and add plenty of evidence on the ability of HM to counterbalance oxidative stress in the newborn infant. Since this is a purely observational cohort focusing on neonatal morbidity, it is not possible at this stage to identify specific changes in management that could potentially have led to improved outcomes over time. Rather, our results are hypothesis generating and must be confirmed with prospectively designed studies.

Authors' Contributions

EM: supervision (lead) and writing original draft (lead). SV: conceptualization (lead) and writing original draft (supporting). AL: formal analysis (equal). JP-T & PM: writing—original draft preparation. GG: editing (equal). CG: methodology (equal), and editing (equal). JF: formal analysis (equal) and supervision (lead). All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and has received approval from the Santa Creu i Sant Pau University Hospital, Clinical Studies Ethics Committee on December 20, 2020 with decision number: IIBSP-ENT-2020-152.

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Informed Consent Statement

Since the study was conducted retrospectively, it spans over a period of two decades, and the data was scanned from the patient files, an informed consent form was not obtained from all subjects involved in the study. In these cases, Spanish regulations allow the Institutional Review Board to waive the requirement to obtain any informed consent.

Data Availability Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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Table 1. Background information

Sample characteristics	Study groups		P value[a]
	Any human milk feeding, N=260	Exclusive formula feeding, N=62	
Gestational hypertension	21 (80.7)	6 (9.7)	0.607
Gestational diabetes	8 (3.0)	2 (3.3)	1.000
Chrioamnionitis	63 (24.0)	20 (32.2)	0.218
Group B strep positive mother	36 (13.8)	5 (8.3)	0.512
Gestational age, weeks	38.59 (2.08)	38.01 (2.27)	0.056
Delivery type: vaginal/ C-section	72 (27.4)	(46.6)	0.0052**
Multiple gestation	13 (4.9)	7 (13.2)	0.071
Apgar 1 minute	8 (2)	7 (3)	0,036*
Apgar 5 minutes	9 (1)	9 (2)	1.000
Birth weight, g	3,116 (639)	2,893 (637)	0.010*
Height, cm	48.6 (2.84)	48.22 (2.69)	0.322

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Cranial circumference, cm	33.83 (2.02)	33.37 (1.94)	0.093
Girls/boys	126/136	26/34	0,567

Note: Data expressed as number (%) or mean (standard deviation),

[a]Comparison between neonates with any human milk feeding and exclusive formula feeding

* $p< 0.05$; ** $p<0.01$

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Table 2. Clinical outcomes by feeding type

	Any human milk feeding N=260	Exclusive formula feeding, N=62	P value[a]
Apnea	47 (18.0)	17 (27.4)	0.074
Abnormal alertness state	143 (55.0)	27 (43.5)	0.198
Abnormal muscle tone	118 (45.3)	28 (45.1)	0.886
Convulsions	10 (3.8)	4 (6.4)	0.304
Hypotension	43 (16.5)	16 (25.8)	0.094
Neonatal acidosis	77 (29.6)	24 (40.6)	0.121
Positive blood culture, n (%)	81 (31.1)	18 (29.0)	1.000
Meningitis	20 (10.1)	0/31 (0)	0.084
Type of respiratory support - No support - Oxygen therapy - Noninvasive ventilation - Invasive mechanical ventilation	 190 (72) 14 (5.3) 34 (13) 24 (9.2)	 34 (55) 3 (4.8) 4 (6.5) 19 (31)	0.000067***
Fraction of inspired Oxygen	0.28 (0.16)	0.39 (0.25)	0.0001**

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Hospitalization, days	10 (9)	12 (9)	0.121
Abnormal brain ultrasound	13 (4.6)	1 (1.9)	0.482
Discharge weight, g	3,425 (689)	3,256 (639)	0.083

Note: Data expressed as number (%) or mean (standard deviation),

[a]Comparison between neonates with any human milk feeding and exclusive formula feeding

* p< 0.05; ** p<0.01; ***p<0.001

Table 3. Multivariate logistic regression analysis of factors associated with higher respirato support

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Variable	Odds ratio	Standard error	z	P>|z|	95% CI
Human milk feeding	0.449	0.157	-2.28	0.023	0.225 to 0.893
Weeks of gestation	0.821	0.051	-3.12	0.002	0.725 to 0.929
Sepsis score	3.668	1.430	3.33	0.001	1.708 to 7.877
Abnormal alertness state	1.576	0.334	2.15	0.032	1.040 to 2.388
Abnormal muscle tone	3.239	1.089	3.49	0.000	1.675 to 6.261
Meningitis	0.505	0.126	-2.73	0.006	0.310 to 0.825
Abnormal brain ultrasound	5.473	2.491	3.73	0.000	2.242 to 13.358

Abbreviations: CI, Confidence Interval; P>|z|, Corresponding Probability for the Reduced Logistic Model; z, Estimated Z-Score.