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Original Article

Own Mother's Milk Protects against Necrotizing Enterocolitis, Sepsis and Poor Outcome of Preterms

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Abstract:
Introduction: Necrotizing enterocolitis (NEC) is a major cause of mortality among premature babies. It has no definitive pathogenesis and no specific treatment. Its prevention remains the most important intervention till now.
Aim of the work: To detect the impact of using mother's own milk to feed preterm babies (< 37 weeks) on necrotizing enterocolitis, occurrence of signs of feeding intolerance, sepsis and mortality.
Methods: This prospective cohort study enrolled 250 preterm babies (< 37 weeks) whose gestational ages ranged from 27-36 weeks who were admitted to the neonatal intensive care unit (NICU) of Kasr Al-Ainy Hospital, Cairo University soon after birth. Mothers with no contraindication to breast feeding were included in the "case" group and the others were included in "control" group.
Results: The mean± SD gestational age of the case group (120 preterm) was 33.12 ± 1.63 weeks and of the control group (130 preterm) was 32.17 ± 1.95 weeks. The mean birth weights of the case and control groups were 1.86 ± 0.49 and 1.55 ± 0.32 kgs, respectively (p= 0.000). The case group showed significant decrease in the incidence of NEC (5% in the case group versus 13% in the control group (p= 0.027). Sepsis incidence also decreased among patients in the case group (37.5% in the case group versus 60% in the control group (p= 0.00). There was no significant difference between the two groups regarding time at which trophic feeding was started but the study group showed significantly shorter duration to reach both minimal enteral nutrition (20cc /kg) (6.85 ± 3.16 days versus 11.20 ± 7.05 days in the control group) (p= 0.000) and full feeds (10.60 ± 3.94 days versus 15.47 ± 8.85 in the control group) (p= 0.000). The mean duration of total parenteral nutrition was significantly shorter in the case group (p= 0.020). The difference between the need for antibiotics in both groups was insignificant (p= 0.353). However, the duration of antibiotic therapy was significantly shorter in the case group (p= 0.000).
Conclusion: Preterm mother's own milk feeding (not necessarily exclusively) proved to be protective against NEC, sepsis and poor outcome.

Level of Evidence of Study: IIA (*1*)**.**
Keywords: Necrotizing enterocolitis; own mother's milk; preterm infants; sepsis; breast milk.
Abbreviations: DM: diabetes mellitus; DVT: deep venous thrombosis; HMOs: human milk oligosaccharides; HTN: hypertension; NEC: necrotizing enterocolitis; NICU: neonatal intensive care unit; SD: standard deviation; SLE: systemic lupus erythematosus; TPN: total parenteral nutrition.

Introduction

Necrotizing enterocolitis (NEC) is a major cause of mortality among preterm babies. It is a disease with variable degrees of intestinal inflammation of multifactorial etiology. The most important risk factors include: prematurity, formula feeding and intestinal dysbiosis (*2*). The clinical presentation is nonspecific and may range from non-specific signs of feeding intolerance to very serious illness with multi-organ failure up to death (*3*). In addition to NEC, preterm infants are more at risk for serious morbidities as early and late onset sepsis with increased mortality rates (*4*). Breast milk is the optimal nutritional option for both preterm and full term babies. Moreover it has a positive impact on the infant's immune system and development (*5*). Despite this fact there are many challenges in establishing and maintaining milk supply to the

vulnerable preterm infant. This is mainly due to inadequate maternal education, waiting for stabilization of both the baby and the mother after preterm delivery and difficulty in adherence to this due to infant separation (*6*). We aimed to detect the impact of using mother's own milk to feed preterm babies (< 37 weeks) on the incidence of necrotizing enterocolitis, occurrence of signs of feeding intolerance, sepsis and mortality.

Subjects and Methods

This prospective cohort study was carried out at Neonatal Intensive Care Unit (NICU) of Kasr Al-Ainy Hospital, Cairo University, Egypt during September 2018 to March 2019. The study was approved by High Research Committee, Faculty of Medicine, Cairo University, Egypt. Legal guardian consented to the trial.

Participants

This study included preterm neonates (<37 weeks) admitted to NICU born and admitted to Kasr Alainy Hospital, Cairo University Hospitals, Cairo, Egypt. Neonates with gastrointestinal anomalies or any other major congenital malformation were excluded from the study.

Methods

All enrolled preterms were subjected to antenatal history taking, Ballard score assessment to predict approximately actual gestational age (*7*) and anthropometric measurement. Nutritional education was provided to all mothers whose babies were born preterm and admitted to the NICU. Mothers who decided to breast feed and managed to provide their own (not donor) milk of more than 50 % of their infant daily needs were included in the case group. Mothers expressed their breast milk either by manual expression or by using a manual or an electrical pump. The milk was given to the infants by tube feeding until completion of 34 weeks when suck-swallow-breath coordination allows the baby to directly breast feed. The milk was stored in bottles in the refrigerator (4°C) for less than 48 hours or in the two-door freezer for less than 3 months. The control group included those who were on same exclusive premature formula feeding as their mothers decided not to breast feed or their adherence to regularly providing breast milk was not feasible mainly due to their remote residence. Both groups were fed according to the standard feeding protocol of the unit with early initiation of enteral feeding once the baby is stable within the first 48 hours of birth and standard advancement. Onset of trophic feeding, parenteral nutrition duration, enteral feeding increment and clinical signs of feeding intolerance or NEC in the two groups were detected. Laboratory and radiological investigations of the two groups were recorded.

Statistical Analysis

Data were analyzed using SPSS© Statistics version 24 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as arithmetic mean ± SD. Correlations between variables were detected using Spearman's correlation test. P values ≤ 0.05 were considered statistically significant.

Results

This prospective cohort study was carried on 250 preterm neonate (<37 weeks) admitted to the NICU of El Kasr Al Ainy, Cairo University Hospital, Cairo, Egypt. They were allocated into two groups; a case group (own mother's milk feeding of ≥ 50% n=120) and a control group (n=130). The mean ± SD gestational age of the case group was 33.12 ± 1.63 weeks and the mean gestational age of the control group was 32.17 ± 1.95 weeks. The mean ± SD birth weights of the case and control groups were 1.86 ± 0.49 and 1.55 ± 0.32 kgs, respectively (p= 0.000). The mean ± SD birth lengths of the case and control groups were 43.61 ± 3.44 and 41.16 ± 3.01 cm, respectively (p= 0.000). The mean ± SD birth head circumferences of the case and control groups were 30.60 ± 2.71 and 28.76 ± 1.78 cm, respectively (p= 0.000).

We encountered the following maternal illnesses during pregnancy in the case group; 10.8%, 2.5%, 12.5% and 2.5% had diabetes mellitus, hypertension, preeclampsia and antiphospholipid syndrome, respectively versus 1.5%, 3.8%, 13.1% and 3.1% in the control group, respectively. (Table 1). There was no significant difference between the two groups regarding time at which trophic feeding was started as it was the unit's protocol to start feeding as early as possible but the study group showed significantly shorter duration to reach both minimal enteral nutrition

(20cc /kg) (6.85 ± 3.16 days versus 11.20 ± 7.05 days in the control group) (p= 0.000) and full feeds (10.60 ± 3.94 days versus 15.47 ± 8.85 in the control group) (p= 0.000). (Table 2).

Table 1. Maternal diseases during pregnancy of both groups.

	Preterm Formula Fed group (130 preterm)		Maternally Breast Fed group (120 preterm)		P value
	Number	%	Number	%	
None	89	68.5	63	52.5	0.009
DM	2	1.5	13	10.8	0.001
HTN	5	3.8	3	2.5	0.545
DM + HTN	2	1.5	6	5.0	0.120
SLE	2	1.5	1	0.8	0.608
Preeclampsia	17	13.1	15	12.5	0.890
Antiphospholipid	4	3.1	3	2.5	0.782
Rheumatic heart	1	0.8	0	0.0	0.335
Epilepsy	0	0.0	5	4.2	0.018
DVT	2	1.5	0	0.0	0.172
Autoimmune thyroiditis	0	0.0	3	2.5	0.069
Others*	2	1.5	8	6.7	0.038

*Others include hypothyroidism, thyroidectomy, eclampsia and lung fibrosis.
DM: diabetes mellitus, HTN: hypertension, SLE: systemic lupus erythematosus, DVT: deep venous thrombosis.
P value <0.05: Statistically Significant.

Table 2. Comparison between control and study group regarding time of initiation of feeding, time for achievement of minimal enteral nutrition and time for reaching full feeds**.**

	Preterm formula fed group (130 preterm)	Maternally Breast Fed group (120 preterm)	P value
	Mean ±SD	Mean ±SD	
Time of initiation of feeding (days)	2.11 ± 1.20	2.30 ± 0.89	0.155
Time for achievement of 20 cc/kg (minimal enteral nutrition) (days)	11.20 ± 7.05	6.85 ± 3.16	0.000
Time for Full feeds* (days)	15.47 ± 8.85	10.60 ± 3.94	0.000

P value <0.05: Statistically Significant.
*Full feeds: when enteral caloric intake reaches 120-130Kcal per day.

Table 3. Comparison between control and study group regarding duration of total parenteral nutrition, antibiotics intake and their duration.

		Preterm Formula Fed group (130 preterm)	Maternally Breast Fed group (120 preterm)	P value
		Mean ±SD	Mean ±SD	
TPN (Duration) (days)		9.30 ± 6.14	7.18 ± 3.33	0.020
Antibiotic intake	No	3 (2.3%)	1 (0.8%)	0.353
	Yes	127 (97.7%)	119 (99.2%)	
Duration of antibiotic therapy (days)		15.06 ± 10.30	10.69 ± 5.71	0.000

P value <0.05: Significant
TPN: total parenteral nutrition

The mean duration of total parenteral nutrition was significantly shorter in the case group (p= 0.020). The difference between the need for antibiotics in both groups was insignificant (p= 0.353). However, the duration of antibiotic therapy was significantly shorter in the case group (p= 0.000). (Table 3). Feeding intolerance was diagnosed when there was abdominal distension defined as increase in abdominal girth by two cm or more between feeds (measured before feeding), vomiting, constipation (no passage of stools by 24 hours), presence of residuals (gastric residual volume more than 30% of previous feeding), hematemesis or bleeding per rectum. Incidence of feeding intolerance was higher in the control group (42.3%) compared to the study group (26.7%) (p= 0.009). (Figure 1). Vomiting, abdominal distention, large residual volume and constipation were detected in 6.9%, 23.1, 12.3% and 3.8% of the control group versus 5.8%, 7.5%, 8.3% and 0% in the case group, respectively with (p= 0.725), (p= 0.001), (p= 0.304) and (p= 0.030) respectively. The incidence of proven NEC (stage ≥ IIA according to Bell's staging criteria [7])

was higher in the control group (13%) compared to the study group (5%) (p= 0.027). (Figure 2). The incidence of proven sepsis (diagnosed by positive blood culture) was significant higher among control group 60% compared to case group 37.5% (p= 0.00). (Figure 3). Eighty seven percent of neonates in the study group were discharged home compared to 66% in the control group (p= 0.000). (Figure 4).

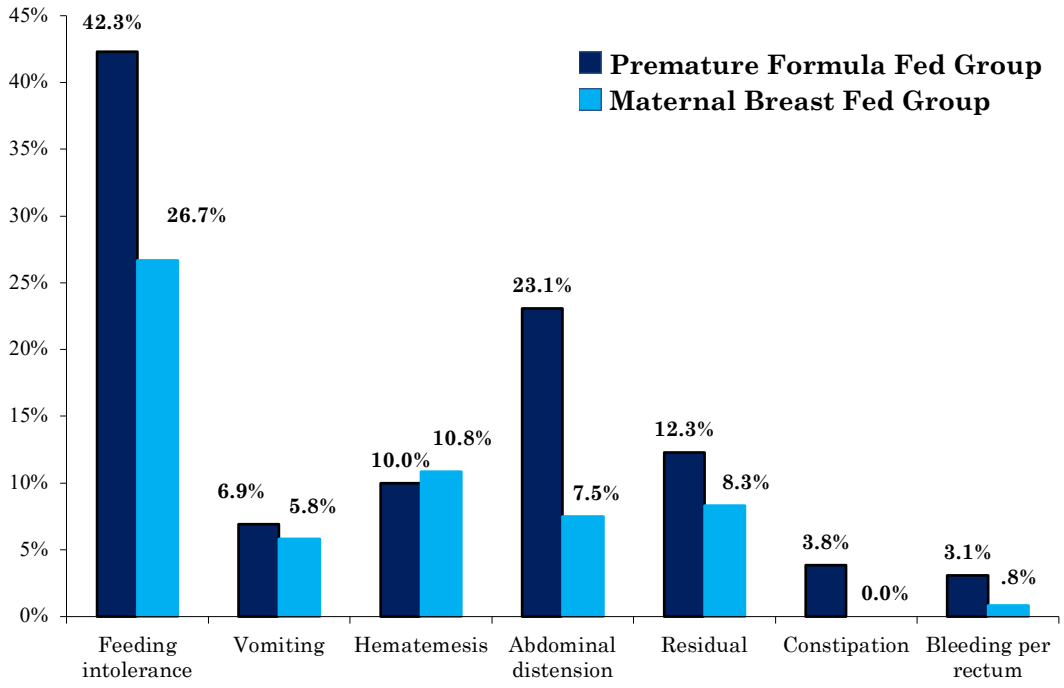

Figure 1. Comparison between Preterm Formula Fed group and Maternally Breast Fed group regarding signs of feeding intolerance.

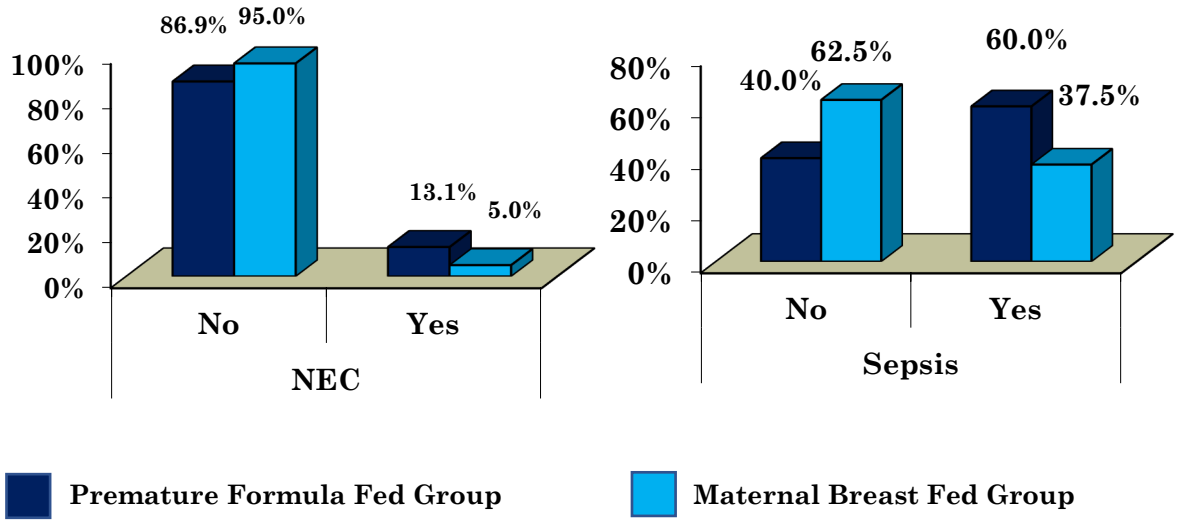

Figure 2. Comparison between the two groups regarding the incidence of proven necrotizing enterocolitis (p = 0.027) and the incidence of proven sepsis (p = 0.00).

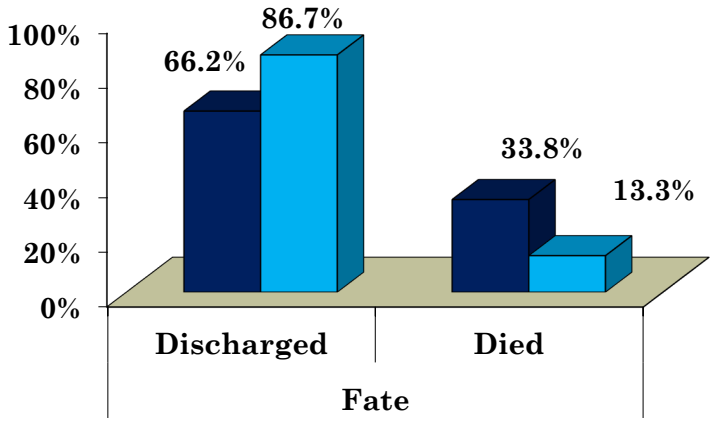

Figure 3. Comparison between the two groups regarding the outcome (p = 0.000).

Discussion

Despite advance in neonatal care, preterm morbidity and mortality remain a burden in both developing and developed countries (*8*). In the present study, there was no significant difference among the case (those who received expressed breast milk ≥ 50% of total feedings) and the control groups regarding age at which feeding was initiated as it is the unit protocol to start feeding early. The case group had significantly lower incidence of feeding intolerance, had reached minimal enteral feeding and full feeds earlier. Breast feeding superiority has always been reported. Researchers have previously documented that preterms who were fed own mother's milk had lower incidence of feeding intolerance compared to those who received donor breast milk and that both groups had lower incidence of NEC than those who received formula feeding (*9*). Results of our work is very encouraging for our practice in NICUs, as breast milk has reduced antibiotic time, protected against NEC and sepsis and improved the outcome. The social and economic burden of complications in preterms is expected to be reduced by implementing maternal breast feeding. Hence, the recommendation of the American Academy of Pediatrics of own mother's milk as the first option for feeding preterm infants followed by donor milk (*10*).

Human milk includes a dynamic diversity of microbiota and other bioactive components as soluble IgA, lactoferrin, lysozymes, human milk oligosaccharides (HMOs), growth factors and cytokines that proved to protect against NEC by enhancing intestinal maturation and reducing inflammation (*11–13*). Recently HMOs have been linked to two signaling pathway responsible for proliferation, development and maturation of the preterm gut (*14*). Recent studies added pooled HMOs to rat models of NEC and found it to be effective in reducing symptoms and decreasing Toll-like receptor 4 (TLR4) expression making it a possible option for treatment not only for prevention (*15–18*). Transforming growth factor- Beta is a constituent of breast milk that was detected at higher concentration in preterm milk especially colostrum and had been suggested to improve feeding tolerance in preterm infants (*19*). Improved feeding tolerance helps infants receive fewer days of total parenteral nutrition (TPN) (*20*). This goes with our results as infants in the case group needed TPN for significantly shorter duration than the control group. Other recently studied protective components are breast milk exosomes which are bioactive components that contain DNA, mRNA and proteins proved to be protective against NEC (*21*). In this study we did not analyze breast milk constituents of the mothers to figure out the responsible component or components for this effect.

In the present study, proven NEC incidence was higher in the control group than in the case group (p= 0.027) providing evidence of the protective effect of breast milk intake. Many other investigators have demonstrated a reduction in NEC incidence with implementation of standardized feeding guidelines in their NICUs (*22–24*). These guidelines have generally incorporated an early minimal enteral nutrition phase, followed by daily advancement based on continued tolerance, increasing human milk use, and decreasing antibiotic and H2 antagonist usage. Protective effect of breast milk against NEC is thought to be dose dependent (*20*, *25*). Clinical studies have demonstrated significant reductions in NEC when infants receive own mother's milk of various durations and doses. Providing own mother's milk of at least 50% of enteral feedings in the first 14 days and greater than 50 mL/kg/day during hospital stay is protective and it has a dose-dependent effect with increased survival time free of NEC with each 10% increase in own mother's milk (*11*).

In the present study, proven sepsis incidence was higher in the formula fed group than in the study group (p= 0.00) confirming that breast milk has immunological benefit compared to formula feeding. Sepsis decreases with breast feeding (*22*), especially if given in the first 5 days of life in very low birth weight infants as it was found to be protective against sepsis up to two months of age [26]. Eighty seven percent of neonates in the case group were discharged home compared to 66% in the formula fed group (p= 0.001) which confirms that mortality increases in preterm infants fed cow's milk protein based formula compared to human milk (*26*). Among the potential limitations to this study is unavailability of having a typical gestational age and weight matched control group as we enrolled neonates in both groups according to maternal desire and health condition that enabled her to provide human milk.

Conclusion

Preterm mother's own milk feeding (not necessarily exclusively) proved to be protective against NEC, sepsis and poor outcome. We strongly advocate for the right of every preterm baby to get the optimum nutrition through his/her own mother's milk and educating both mothers and health care workers about the beneficial effect of breast milk for this vulnerable age group.

Author Contributions: Salma Z. El Houchi contribution: formulation of the research idea and design, revision of the manuscript. Shahenda S. Ismail contribution: data collection and analysis. Esraa A. Elmazzahy contribution: formulation of the research idea and design, interpretation of results and revision of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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