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Abstract

Background: Although highly beneficial, human milk feeding is challenging in preterm infants due to adverse NICU factors for the infant and mother. Aim: To investigate the effects of an early intervention in promoting infant's human milk feeding and acquisition of full oral feeding. Methods: This study is part of a RCT. We included preterm infants born between 25+0 and 29+6 weeks of gestational age (GA) without severe morbidities, and their parents. Infants were randomized to either receive early intervention (EI) or standard care (SC). EI included PremieStart and parental training to promote infant massage and visual attention according to a detailed protocol. SC, in line with NICU protocols, included Kangaroo Mother Care. The time of acquisition of full oral feeding and human milk consumption at discharge were recorded. Results: Seventy preterm (EI n=34, SC n=36) infants were enrolled. Thirteen were excluded according to the protocol. Fifty-seven (EI n=29, SC n=28) infants were evaluated at discharge. The two groups were comparable for parent and infant characteristics. A significantly higher rate of infants fed with any human milk was observed in the EI group (75.9%) compared with the SC group (32.1%) (p=0.001), and EI infants were four times more likely to be fed exclusively with human milk. Full oral feeding was achieved almost one week earlier in EI infants (mean postmenstrual age 36.8±1.6 vs 37.9±2.4 weeks in EI vs SC, p=0.04). Conclusions: Early interventions promoting mother self-efficacy and involvement in multisensory stimulation have beneficial effects on human milk feeding in preterm infants.

Keywords	preterm infant; human milk; feeding; early intervention

Corresponding Author	Camilla Fontana
Corresponding Author's Institution	NICU, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano
Order of Authors	Camilla Fontana, Camilla Menis, Nicola Pesenti, Sofia Passera, Nadia Liotto, Fabio Mosca, Paola Roggero, Monica Fumagalli
Suggested reviewers	Kerstin Hedberg Nyqvist, Renee Flacking, Paula Meier

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EFFECTS OF EARLY INTERVENTION ON FEEDING BEHAVIOR IN PRETERM INFANTS: A RANDOMIZED CONTROLLED TRIAL

Abstract

Background: Although highly beneficial, human milk feeding is challenging in preterm infants due to adverse NICU factors for the infant and mother.

Aim: To investigate the effects of an early intervention in promoting infant's human milk feeding and acquisition of full oral feeding.

Methods: This study is part of a RCT. We included preterm infants born between 25^{+0} and 29^{+6} weeks of gestational age (GA) without severe morbidities, and their parents. Infants were randomized to either receive early intervention (EI) or standard care (SC). EI included PremieStart and parental training to promote infant massage and visual attention according to a detailed protocol. SC, in line with NICU protocols, included Kangaroo Mother Care. The time of acquisition of full oral feeding and human milk consumption at discharge were recorded.

Results: Seventy preterm (EI n=34, SC n=36) infants were enrolled. Thirteen were excluded according to the protocol. Fifty-seven (EI n=29, SC n=28) infants were evaluated at discharge. The two groups were comparable for parent and infant characteristics. A significantly higher rate of infants fed with any human milk was observed in the EI group (75.9%) compared with the SC group (32.1%) (p=0.001), and EI infants were four times more likely to be fed exclusively with human milk. Full oral feeding was achieved almost one week earlier in EI infants (mean postmenstrual age 36.8±1.6 vs 37.9±2.4 weeks in EI vs SC, p=0.04).

Conclusions: Early interventions promoting mother self-efficacy and involvement in multisensory stimulation have beneficial effects on human milk feeding in preterm infants.

Keywords: preterm infant; human milk; feeding; early intervention

Abbreviations:

BPD - Bronchopulmonary dysplasia
CRIB - Clinical risk index for babies
cPVL - cystic Periventricular leukomalacia
cUS - cranial Ultrasound
EI - Early intervention
GA - Gestational age
GMH - IVH Germinal matrix hemorrhage-Intraventricular hemorrhage
KMC - Kangaroo mother care
NCPAP - Nasal continuous positive airway pressure
NEC - Necrotizing enterocolitis
NICU – Neonatal intensive care unit
NIDCAP - Newborn individualized developmental care assessment program
ROP - Retinopathy of prematurity
SC - Standard care
SES - Socio economic status
SGA - Small for gestational age

Background

Preterm birth is the leading cause of infant mortality worldwide [1] and it is associated with several neonatal morbidities, the main ones including sepsis, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) and brain lesions [2]. Infants' life quality may also be negatively affected by long-term neurodevelopmental delays [3,4].

In premature infants, breast milk plays a key role with several studies reporting a significant decrease of sepsis and NEC or lower rates of retinopathy of prematurity (ROP) [5–7]. Similarly, it has been demonstrated to positively affect neurodevelopment in the long term, with benefits in motor and cognitive outcomes and neurobehavioral organization [8,9].

Therefore, exclusive human milk is recommended by the American Academy of Pediatrics as the first choice for preterm infants' enteral nutrition, especially during the first six months of life [10].

However, preterm birth and admission to a Neonatal Intensive Care Unit (NICU) are the strongest predictors of not being exclusively breastfed at discharge [11]. Vohr et al. reported that 78% of mothers initiate human milk feeding in the NICU, but only 31% provide it at discharge [12].

Human milk feeding is particularly challenging for preterm infants and their mothers because of the negative factors they are exposed to, such as the NICU environment, neonatal morbidities, the paucity of parental contact, delayed breastfeeding, and other factors [13]. All of these factors can affect the mother-infant relationship, which is essential for starting and continuing lactation [14,15]. An established practice to improve the mother-infant relationship in NICU is Kangaroo Mother Care (KMC), and its benefits on breastfeeding are well-known [16]. Skin-to-skin contact promotes a greater closeness between infant and mother, helping her to interpret infant cues [17]. The potential beneficial effects of a more active tactile contact, such as preterm baby massage, have been recently suggested to have ~~:~~ a positive impact on infant neurodevelopment [18,19] and ~~or~~ duration of hospital stay[20], although the reported evidence~~s~~ related to the latter issue are still ~~contrasting~~ inconsistent [21,22].

Moreover, early intervention strategies, including infant massage, have been proved to be effective on sensitive and responsive interactions between preterm infants and their mothers [22,23], as documented by recently published RCTs [22,23].

However, the effects of an early multisensory intervention that includes preterm baby massage and early mother-infant interaction on infant's feeding behavior have not yet been investigated.

The present study is part of an RCT aimed at assessing the effectiveness of an early intervention program in promoting visual function and neurodevelopment in preterm infants. Within this context, further analyses have been performed, with the exploratory purpose of investigating the effect of the early intervention in promoting infants' milk feeding and acquisition of full oral feeding.

Methods

Subjects

The trial was approved by the Ethics Committee Milano Area B on the 14th of March 2014. Written parental informed consent was obtained from the parents.

All of the preterm babies, consecutively born between 25^{+0} and 29^{+6} weeks gestational age (GA) from April 2014 to January 2017 at the same institution, were eligible for the study. Exclusion criteria were as follows: multiple pregnancy (triplets or higher); genetic syndromes and/or major congenital malformations; NEC stage III according to Bell [24]; and major brain lesions, including Germinal Matrix Intraventricular Hemorrhage (GMH-IVH) > 2° grade according to Papile [25], documented by early cranial ultrasound (cUS). Infants who developed stage II NEC were also excluded from the present exploratory study due to the potential adverse effect of any stage of NEC on oral feeding acquisition related to the protracted suspension of oral feeding.

Mothers were selected according to the following inclusion criteria: age over 18 years, good comprehension of the Italian language, no single-parent families, no obvious cognitive impairments or

psychiatric disorders, and no drug addictions.

Infants were recruited after the first week of life and if clinically stable (no need for invasive mechanical ventilation and no active sepsis).

Study design

This study is part of a larger RCT (Trial Registration Number: NCT02983513).

Infants were randomized either to receive Early Intervention (EI) or Standard Care (SC) using sealed envelopes prepared in groups of 10 through computer-generated randomization. Twins were considered together for the randomization, as the EI program was mainly parent-based.

The EI program was delivered in addition to routine care during the NICU stay by the same investigator, according to the PremieStart Protocol [26], to train parents to: recognize signs of infant stress and alert-available behavior to promote mother-infant interaction; adopt principles of graded stimulation; and optimize interactions and avoid overwhelming infants through facilitation strategies (for example, engage and support the visual attention of the newborn). The program was held in eight main sessions and one additional post-discharge session. In addition, parents were trained and invited daily to promote preterm baby massage therapy and visual attention when babies were in an alert or active behavioral state according to Brazelton [27]. A daily diary was given to parents to register the interventions. Preterm baby massage therapy was performed twice a day by parents after receiving two training sessions and not before both 30 weeks postmenstrual age and 10 days of postnatal life. Each massage session consisted on 10 minutes of slow tactile stimulation of the back, applying moderate-pressure stroking with both hands. During the massage, the infant was placed in the prone position. Each session was performed at least 2 hours after the previous one.

Parents promoted visual attention at least once a day using either a black and white toy or the parent's face. This interaction took place when the baby was in an alert behavioral state and not before 34 weeks

of postmenstrual age. Infants were supine, either on the parent's lap or in their crib, and were nested with a blanket to avoid excessive stimulation.

SC, according to the NICU protocols, included KMC, nesting and minimal handling. During the study period, no specific interventions to decrease stress (e.g., Newborn Individualized Developmental Care Assessment Program - NIDCAP) were in use.

KMC was part of the clinical routine practice for both groups and it was started as soon as infants were weaned from mechanical ventilation regardless of the randomization group.

The baseline characteristics of the two groups were collected from hospital charts. Recorded data included: gender, birth weight and GA, Small for Gestational Age (SGA) [28], twin birth, mode of delivery, Apgar scores at 1 and 5 minutes, Clinical Risk Index for Babies (CRIB) [29], number of days on invasive mechanical ventilation or on nasal continuous positive airway pressure (NCPAP) or high-flow nasal cannula, duration of hospital stay and postmenstrual age at discharge.

The following neonatal morbidities were considered: ROP [30], BPD [31], GMH-IVH [25] and sepsis (increased plasma levels of C-reactive protein associated with a positive blood culture).

Family socio-economic status (SES) was calculated and classified according to Hollingshead's criteria [32].

The feeding protocol of the unit was the same during the study period, and all mothers were provided with a pump and encouraged to start pumping on day 1 after birth and to increase the pumping interval to every 3 hours.

In case of unavailable or insufficient human milk, formula feeding was started. Infants' human milk intake at discharge was calculated from the infants' computerized medical chart, completed by nurses blinded to group allocation and expressed as a percentage of the total milk intake. When infants were breast fed, mothers were asked to weight their baby before and after each feeding so that the volumes consumed by the baby could be calculated. Infants were categorized as receiving exclusive formula,

exclusive human milk and human milk plus formula, and the data are presented accordingly.

For further analysis, infants fed any extent of human milk, irrespective of the quantity or the exclusivity, were categorized as fed any human milk [10].

Fortification of human milk was started when the enteral intake reached 90 ml/kg/day. The volume of enteral feeding was increased based on the infants' cardio-respiratory stability and gastrointestinal tolerance. Human milk was fortified with a target fortification to comply with the guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). The target levels of the human milk macronutrients were as follows: 3 g/100 ml of protein, 8.8 g/100 ml of carbohydrate and 4.4 g/100 ml of fat [33].

Statistical analysis

All data were analyzed with R software, version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were compared by Fisher's exact test and continuous variables by Mann-Whitney U test. A P value < 0.05 was considered as significant.

Results

A total of 70 infants (EI n=34, SC n=36) were recruited between April 2014 and January 2017.

According to the protocol, 3 infants allocated to EI did not receive treatment because 2 developed stage III NEC and 1 family became a single-parent family after written informed consent was signed by both parents. All babies in the SC group received their allocated treatment as part of routine clinical practice.

At discharge, 10 infants (EI n=2; SC n=8) were excluded from feeding behavior evaluation: 5 infants in the SC group developed NEC (stage II n=3, stage III n=2), and 5 mothers (EI n=2; SC n=3) decided not to express milk from day one.

Therefore, 57 infants (EI n=29, SC n=28) were eligible for evaluation on type of feeding at discharge.

Parental and infant characteristics were similar between the two groups (Table 1).

Table 1. Baseline characteristics of the EI and SC groups

Demographic feature	**Early intervention (n=29)**	**Standard care (n=28)**	**P value**
Gestational age at birth (weeks), mean±SD	28.1 ± 1.3	27.6 ± 1.5	0.09 *
Birth Weight (g), mean±SD	1020 ± 274	1040 ± 322	0.91 *
Male, n (%)	13 (44.8%)	13 (46.4%)	1.00 °
Singleton, n (%)	18 (62.1%)	15 (50%)	0.43 °
CRIB II score, mean±SD	8.0± 2.3	8.6 ± 2.6	0.42 *
Apgar score at 1', median (range)	7 (4-9)	6 (2-8)	0.17 *
Apgar score at 5', median (range)	8 (6-10)	8 (5-9)	0.14 *
Cesarean section, n (%)	26 (89.7%)	23 (82.1%)	0.47 °
Days of mechanical ventilation (prior to recruitment), mean±SD	3.8 ± 6.5	6.6 ± 10.0	0.17 *
Days of NCPAP, mean±SD	27.4 ± 15.3	27.1 ± 12.9	0.82 *
Days of high-flow nasal cannula, mean±SD	10.8 ± 20.4	11.3 ± 19.4	0.78 *
Small for gestational age, n (%)	8 (27.6%)	9 (32.2%)	0.77 °
Sepsis, n (%)	13 (44.8%)	11 (39.3%)	0.79 °
ROP			0.42°
stage I-II	1 (4%)	4 (14%)	
stage III	3 (10%)	3 (11%)	
Severe bronchopulmonary dysplasia, n (%)	9 (31%)	7 (25%)	0.77 °
GMH-IVH 1-2, n (%)	2 (6.9%)	3 (10.7%)	0.67 °
Maternal age (years), mean±SD	33.4 ± 4.2	33.6 ± 5.9	0.81 *
SES, mean±SD	50.3 ± 9.6	43.6 ± 13.3	0.06 *

Postmenstrual age at recruitment (weeks)			
mean±SD	29.7 ± 1.5	29.6 ± 1.3	0.46 *

* Mann-Whitney U Test, ° Fisher's Exact Test

In the EI group the massage therapy was started by parents at 31.8 ± 1.5 weeks of postmenstrual age (mean ± SD) and visual interaction was proposed starting from 34.9 ± 0.7 (mean ± SD) weeks of postmenstrual age.

No differences were found between the two groups in terms of length of stay (75.3±21.1 vs 85.9±33.2 days in the EI and SC groups, respectively, p=0.35) and postmenstrual age at discharge (38.9±3.0 vs 39.9±3.8 weeks in the EI and SC groups, respectively, p=0.36).

The feeding characteristics of the two groups are described in Table 2.

Table 2. Feeding characteristics of the EI and SC groups.

	Early intervention (n=29)	**Standard care (n=28)**	**P value**
Postmenstrual age at acquisition of full oral feeding – from birth (weeks), mean±SD	36.8 ± 1.6	37.9 ± 2.4	0.04 *
Percentage of human milk consumption, mean±SD	57.6 ± 41.6	22.9 ± 36.9	< 0.001*
Type of feeding at discharge, n (%)			0.003 °
Exclusive Human Milk	12 (41.4)	3 (10.7)	
Human Milk + Formula	10 (34.5)	6 (21.4)	
Exclusive Formula	7 (24.1)	19 (67.9)	

* Mann-Whitney U Test, ° Fisher's Exact Test

Infants enrolled in the EI group achieved full oral feeding almost one week before SC infants ($p=0.04$) and showed a higher consumption of human milk at discharge ($p<0.001$).

More specifically, a higher rate of babies fed with any human milk was observed in the EI group compared with the SC group (EI=75.9% versus SC=32.1%, $p=0.001$), and EI group babies were four times more likely to be fed exclusively with human milk.

Discussion

Our findings suggest that early intervention strategies, based on a parental training program, are successful in improving human milk feeding in preterm infants at discharge. Accordingly, the EI program resulted in a higher proportion of infants exclusively fed with human milk compared with the SC group. This result is of primary importance given the widely acknowledged beneficial effects of breast milk for the short- and long-term outcomes of preterm infants [5,6,8].

The lactation rates observed in the SC group are consistent with those previously reported in infants with similar GA [12], whereas mother's milk consumption in the EI group was approximately four times higher.

The percentage of human milk intake was assessed at discharge, thus supporting the hypothesis that the EI program may contribute not only to sustain initiation but also to maintain lactation until term age.

Both components (PremieStart, the parental training program, and infant massage) of our early intervention program may be involved in the observed beneficial effect on the mother's lactation. However, due to the combined nature of our intervention, it is not possible to disentangle each single contribution.

PremieStart [26] is based on the promotion of the mother-infant relationship through facilitation strategies that help parents recognize signs of alert and stress behavior. This program, together with its

original version, the Mother Infant Transaction Program (MITP) [34], has been proven to encourage mother's responsiveness and to reduce stress and depressive symptoms [23,26,35], thus theoretically promoting the attainment of the maternal role, which is threatened in cases of preterm birth.

The second major element of our protocol is infant massage delivered by parents and mainly by mothers during the NICU stay, which has also been reported to be effective in reducing depressed mood and anxiety in mothers of preterm infants [36].

We hypothesize that both elements of the intervention contributed to sustain mother milk provision. This hypothesis is in line with studies showing how parental participation and involvement are of crucial importance for maintaining breastfeeding [37,38] and with research on how depression and stress could negatively affect breastfeeding [39].

Another significant result of the present study is the effect on the timing of the acquisition of full oral feeding. Infants in the EI group showed a mature oral feeding pattern approximately one week corrected age before infants in the SC group. This finding may be partially explained by the attainment of one of the objectives of PremieStart, namely, training parents to recognize signs and to respond to infant cues in daily care, which is reported to enhance the development of preterms' oral skills [40,41].

The observed beneficial effects of EI did not result in a shortened NICU stay. This finding is in contrast with a wide meta-analysis published in 2004 reporting that massage intervention in preterm infants (GA <37 weeks and/or birth weight <2500g~~r~~) decreased the average length of stay by 4.5 days. However, the same meta-analysis reported concerns about the methodological robustness and blinding of this outcome [42]. More recent studies have investigated the length of stay after massage intervention in preterm infants but results are not conclusive [20,43]. Additionally these studies were performed on more mature infants [43] or infants suffering milder postnatal morbidities [20] compared to our group. We focused on preterm infants (<30 weeks gestation), and although babies with major morbidities were excluded, all of them experienced postnatal complications, in particular severe BPD and sepsis, potentially prolonging

the time needed to acquire physiologic stability and full respiratory competency, which are mandatory for home discharge [44].

Previous studies report a beneficial effect of human milk in reducing the occurrence of NEC; however, this effect could not be evaluated, as NEC was defined as an exclusion criterion of the study.

One of the advantages of the present study is that medical staff members completing infants' computerized charts were blinded to group allocation.

One limitation of the study is represented by the failure to differentiate between human milk feeding and breastfeeding, as this information was not clearly available in the dedicated nutritional section of the infants' computerized medical chart.

Another possible limitation is the lack of a baseline evaluation of mothers' psychosocial aspects; however, the randomization supports the homogeneity of the two groups.

Based on previous reports [45], the slightly higher SES observed in the EI group could have influenced human milk feeding rates; however, this difference is not statistically significant. Maternal age, one of the most reported limiting factors for human milk feeding in preterm infants [11], was similar between the two groups.

Conclusions:

Even if preliminary, our RCT highlights the role of early intervention strategies in promoting human milk feeding. Early approaches promoting maternal self-efficacy and involvement in a multisensory stimulation to enhance mother-infant closeness and the dyadic relationship should be implemented in the care of preterm infants in addition to standard care.

Conflicts of interest:

Authors have no conflicts of interest to declare.

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