



Tolerance in Preterm Infants Fed Exclusively with Human Milk. Prospective Analytic Study

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Abstract

Human milk is the best feeding for premature infants. When Own Mother's Milk (OMM) is insufficient or unavailable, the alternative is represented by the Donor Milk (DM). OMM and DM must be fortified to support the adequate growth.

Objectives: Evaluation of the food tolerance on preterm fed exclusively with fortified Human Milk (HM).

Materials and Methods: This prospective analysis has been performed on a sample of 48 preterm with GA \leq 32 weeks. Gastric Residual (GR), Vomiting (V) and Feeding Suspension (FS) are the parameters performed. We identified two categories (OMM/DM) and 4 groups: newborns fed exclusively with OMM (EOMM), with prevalent OMM (POMM), with exclusively DM (EDM) and with prevalent DM (PDM).

Results: The overall incidence of GRs was 18%, the incidence of bilious residuals was 4%, the incidence of Vs was 4.5%, there was no indication of blood in the stool, the total percentage of days of FS was 12.7%. There was no statistical correlation between the incidence of GR, V, FS in the two categories (OMM/DM). The relationship between the kind of feeding and the GA or the BW was not statistically significant.

Conclusions: The study highlights the irreplaceability of the OMM in feeding the preterm and that the DM is a valid substitute of OMM.

Keywords: Preterm feeding, Donor human milk, Food tolerance.

Abbreviations: OMM-Own Mother's Milk, DM-Donor Milk, HM-Human Milk, HMB-Human Milk Bank, AIBLUD-Italian Association of Milk Banks, NEC-Necrotizing Enterocolitis, GA-Gestational Age, BW-Birth Weight, VLBW-Very Low Birth Weight, ELBW-Extremely Low Birth Weight, EOMM-Exclusively Own Mother's Milk, POMM-Prevalent Own Mother's Milk, EDM-Exclusively Donor Milk, PDM-Prevalent Donor Milk, GR-Gastric Residual, V-Vomiting, FS-Feeding Suspension, NICU- Neonatal Intensive Care Unit.

Introduction

The premature birth affects 10% of deliveries; thanks to the advanced assistance technologies, the survival, even at the GA (22-23 weeks) considered unthinkable in the past, is now possible. Premature infants are at high risk of serious complications such as NEC. It is one of the most dangerous pathologies linked to prematurity because it is encumbered with a mortality ranging from 10 to 50% [1]. Currently, the feeding with the breast milk is referred to as one of the most important and effective prevention strategies of NEC.

A protective effect of the mother's milk has also been demonstrated against other complications of prematurity such as retinopathy of prematurity, broncho-pulmonary dysplasia and sepsis. Equally important are the beneficial effects that the breast milk can have on the quality of neurological development of the preterm infant [2-21]. Several studies show a direct relationship between the quantity and the duration of the feeding with the breast milk and the neurological performance, even some years later. This is particularly relevant for this category of children who are at high risk of negative neurological

outcomes. The use of the OMM improves the food tolerance and reduces the duration of the parenteral nutrition by favoring the fastest achievement of exclusive enteral feeding and reducing the risk of infections related to the use of central venous catheters. Structured promotion of breast milk expression is associated with shortened hospitalization for very preterm infants [21-25].

These effects of the breast milk are attributable to the wealth of bioactive components, highlighted by the new technologies in the biological field, including stem cells. These factors favor the development and the maturation of organs and systems, first of all the intestines. That's the reason why the breast milk is considered the best choice for the premature baby and is often referred to as an "essential drug" [26-38]. When the mother's milk is not available, the alternative is represented by the human milk devoted to the banks by generous donors. In Italy there are currently 38 milk banks coordinated by Italian Association of Milk Banks (AIBLUD). The treatment of the DM partly reduces the biological heritage of the mother's milk and also the

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macronutrient composition. However, clinical practices demonstrate that many beneficial properties of DM still persist after treatment [39-44].

OMM and even more DM have a protein and caloric content that is not adequate to support the growth that should be similar to the intrauterine growth, especially the brain that is very sensitive to nutritional deficiencies during the last trimester of pregnancy. For this reason human milk must be adequately fortified. In particular increased protein intake may provide short and long term benefits in terms of growth and neurodevelopment in human milk-fed ELBW infants [45-49].

In the NICU of “Casa Sollievo della Sofferenza”, for premature babies weighing less than 1800 grams only the HM is used, OMM or DM from “Allattiamolavita”, the HMB operating for 10 years. HM is fortified when the enteral volume of 60ml/kg is reached. The individualized fortification, based on the evaluation of the macronutrient content of human milk (the human milk analyser (HMA, Miris AB®, Uppsala, Sweden), is used.

Objectives

- Evaluation of the food tolerance and of the incidence of NEC on premature infants of GA≤32 weeks fed during the NICU hospitalization exclusively with fortified HM.
- Evaluation of any statistical significance in the comparison between the two kinds of feeding, with OMM and EDM in the frame of symptoms related to the food tolerance.
- Assessment of possible statistical significance regarding the use of OMM and/or DM with respect to GA and BW.

Materials and Methods

This prospective analysis has been performed in the period from January 2016 to June 2017 on a sample of 48 premature infants with GA≤32 weeks. Infants with congenital malformations or congenital infections were not enrolled. All donors signed a written informed consent to donate their milk to clinical or research use therefore the ethics committee of Author's Institution ruled that no formal ethics approval was required in this particular case. The milk is administered every 2 hours for newborns weighing <1250 grams and every 3 hours for those of a higher weight.

We identified 4 groups-newborns fed with Exclusively Own Mother Milk (EOMM), newborns who received Prevalent Own Mother Milk (POMM), newborns who received Exclusively Donor Milk (EDM) and newborns who received Prevalent Donor Milk (PDM). The evaluation of the following parameters was performed in relation to the food tolerance-Gastric Residual (food/bilious) (GR), Vomit (food/bilious) (V) and days of Feeding Suspension (FS). The collected data have entered in a specific database.

Additional group comparisons were carried out between newborns who received EMOM or PMOM and newborns who received EDM or PDM using two-sample un-paired t-test. Continuous variables were reported as mean ± standard deviation while categorical variables were reported as frequency and percentages. A p-value <0.05 was considered as statistical significant. All analyses were performed using SAS (SAS institute, Cary, NC, USA). A further evaluation concerned the number of newborns fed with different modalities- OMM for the duration of the stay in NICU, OMM for the first days of life plus DM to cover the entire demand, only DM, and finally, the total amount of DM used to feed these preterm infants before the availability of their mother's milk or in its absence (Tables 1, 2, 3 and 4).

We didn't analyze the feeding with preterm formula because this kind of milk is used only for infants in discharge fed with DM and it is not ethically possible to steal the milk from mothers or from the bank for the sole purpose of carrying out a study. The results have been divided into population data and tolerance data.

Results

Data on Population

The population includes 48 preterm infants of GA ≤ 32 weeks-there's one case of a high preterm delivery of 23 weeks, 3 of 24 weeks, 2 of 25 weeks, 5 of 26 weeks, 6 of 27 weeks, 3 of 28 weeks, 4 of 29 weeks, 8 of 30 weeks, 10 of 31 weeks and 7 of 32 weeks. Regarding the BW, the study sample includes 15 newborns weighing <1000grams, 27 newborns with BW between 1000 gr and 2000 grams and 5 newborns weighing >2000grams. 29 are the VLBW infants (BW<1500grams) (Figure 1, Table 3).

The period of hospitalization is proportionate to the GA and to the BW with an average of 73.75 days (min 33, max 93) for the newborns weighing <1000 grams, of 42.96 days for those having a wide range and weighing between 1000 and 2000 grams (min 16, max 113) and of 21.25 days for those born weighing >2000grams (18-29 days). Regarding the GA, the average is 39 days (min 18, max 113) for those born between 28 and 32 weeks of GA, and 71.7 days (min 27, max 109) for infants between 23 and 27 weeks.

Distinguishing the categories of infants according to the feeding, 5 preterm were fed with EOMM (including 3 VLBW), 17 newborns were fed with POMM (including 10 VLBW and 6 ELBW), 12 newborns received EDM (6 VLBW and 4 ELBW) and 14 received PDM (10 VLBW and 4 ELBW). 22 (44%) preterm infants were fed with EOMM or POMM and 26 (52%) with EDM or PDM. For the category of ELBW, 6 newborns on 15 (40%) weighing <1000grams were fed with OMM (exclusive or predominant). The amount of OMM used was 19271 ml for 22 children (44% of the population), while the amount of DM was 16414 ml (52% of the population) (Figure 1 and Table 1).

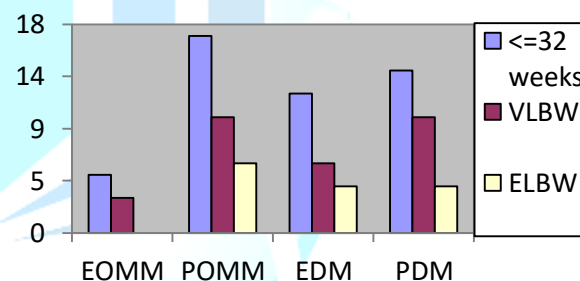


Figure 1: Distribution based on gestational age. EOMM-Exclusive Own Mother's Milk, POMM-Prevalent Own Mother's Milk, EDM-Exclusive Donor Milk, PDM-Prevalent Donor Milk, VLBW-Very Low Birth Weight (<1500grams), ELBW-Extremely Low Birth Weight (<1000grams).

Data on Tolerance

39 (81.2%) newborns presented GR; 15 of them (38.4%) suffered for a number of days <5, 8 of them (20%), between 6 and 15 days and the remaining 25 (64%) >15 episodes with a maximum of 36 (a 650grams patient hospitalized for 109 days). In total, 457 events have been recorded, corresponding to 18% of days of hospitalization (2464); bilious GR characterized 100 days corresponding to 21.8% of the total case of the GRs and 4% of the total events (Tables 1,2,3 and 4).

The highest number of episodes concerned ELBW with 322 episodes, hence 70.4% of the total; the number of V, related to 27 infants was 111 (56.2%) and 20 of them (74%) reported a number of events <5, after 3 of them between 5 and 10, and 2 of them with 13 events. If we compare the tolerance to the kind of milk, 21 newborns (43.8%) reporting the gastrointestinal symptoms were fed with the DM-11 of them (22.9%) with EDM, 10 (20.8%) with PDM; 15 newborns (31.25%) were fed with OMM, 3 of them (6.25%) with EOMM and 12 (25%) with POMM.



The number of GRs was 289 (63.2%) for those fed with the DM- 178 (39.9%) (range 1-31) received EDM and 111 (24.28%) (range 1-20) PDM. The total for those fed with OMM was 160 (35%) -12 (2.6%) EOMM and 148 (32.3%) with POMM. Regarding the symptom of V, 15 newborns (31.25%) fed with DM were reported-9 of them (18.74%) (range 1-13) EDM and 6 (12.5%) PDM. Moreover, 12 newborns fed with OMM are to be distinguished into 4 (8.33%) with EOMM and 8 (16.6%) with POMM. 60 events of Vs (53.56%) occurred among those fed with DM-37 of them (33%) (1-13) with EDM and 23 (20.5%) (range 1-13) with PDM. The other 58 events of V (51.57%) with OMM concerned 26 (23.2%) (range 1-5) with EOMM and 32 (28.57%) (1-5) with POMM.

If we relate this data to the suspension of feeding, on the basis of the internal NICU guidelines, the total days of FS during the hospitalization for the entire population is 96 out of 2464 (3.8%) and involves 17 newborns (35%)-in detail, the suspension lasted 1 day for 2 newborns, 2 days for other 6, 4 days for 2 of them, 6/8 days for 3, 2 weeks for 2 newborns, and in one case 20 days. According to the kind of feeding, 56 days of FS have been recorded-58.3% of the FS occurred among those fed with DM, 33 of them (34.3%) (range 1-7) were fed with EDM and 23 (23.9%) (range 2-14) with PDM. No day of FS has been recorded for those fed with EOMM and 29 days (30.2%) (range 2-22) for those fed with POMM.

If we concentrate on the VLBW (<1500grams), on a total of 338, 15 of them (48.38%) reported the symptoms and were fed with DM- 7 (22.5%) EDM and 8 (25.8%) PDM. Among those fed with OMM, 13 cases occurred-3 (9.67%) with EOMM and 10 (32.2%) with POMM. Regarding the number of GR, 179 were detected among newborns who received DM-102 (30.1%) with EDM and 77 (22.7%) with PDM. Among those who received mother's milk, 159 cases (47%) were

highlighted-12 (3.5%) with EOMM and 147 (43.49%) with POMM. Concerning the vomit, we recorded 60 daily observations for those fed with DM-23 (27%) with EDM and 31 (35.6%) with PDM. The cases of those who received OMM, were 26 (30.5%)-in detail, 12 (14, 1%) were fed with EOMM and 14 (16.4%) with POMM.

The days of suspension were 60 (68.9% of the total) for newborns who received DM-29 (33.3%) with EDM and 31 (35.6%) with PDM. For those fed with EOMM, there were no days of suspension; instead, 27 days (31%) have been registered where OMM was prevalent.

In the population of 48 premature newborns of GA ≤ 32 weeks fed only with human milk-

- There were no cases of NEC,
- The overall incidence of grs was 18%,
- The incidence of bilious residuals was 4%,
- The overall incidence of Vs was 4.5%,
- There was no indication of blood in the stool,
- The total percentage of days of FS was 12.7%,
- There are differences between those fed with EOMM/POMM or EDM/PDM-
- The incidence of gastrointestinal events resulted very low in The group of Those fed EOMM (2.6% GRs, 8.3% V) and There was no day of suspension of The enteral feeding (**Table 1,2,3**),
- There was no statistical correlation between The incidence of GR and V, The number of days of feeding suspension and The duration of The hospitalization between The two categories (OMM/DM),
- The correlation between the kind of feeding and the GA or the BW was not statistically significant (**Table 4**).

N° preterms	EMOM	%	PMOM	%	EDM	%	PDM	%
GR	3	6.25	12	25	11	22.9	10	20.8
V	4	8.33	8	16.6	9	18.74	6	12.5
FS	0	0	29	30.2	33	34.3	23	23.9

Table 1: Distribution of symptoms based on the type of milk (number of preterm infants).

N° events	EMOM	%	PMOM	%	MOM	EDM	%	PDM	%	DM
GR	12	2.6	148	35	160	178	39.9	111	24.28	289
V	26	23.2	32	28.57	58	37	33	23	20.5	60
FS	0	0	29	30.2	29	33	34.3	23	23.9	56
	38		209		247	248		157		405

Table 2: Distribution of symptoms based on the type of milk (N° events).

Variable	Category	All Subjects
N°		48
Milk category	DM	26 (54.17)
	OMM	22 (45.83)
Hospitalization days		50.94 \pm 25.85
GA		28.96 \pm 2.54
FS days		2.00 \pm 4.38
BW		1366.94 \pm 509.57
GR		9.52 \pm 10.36
V		2.33 \pm 3.35

Table 3: Variables analysis.

Variable	DM	MOM	p-value	Odd Ratio
N°	26	22		
Hospitalization days	53.15 \pm 26.37	48.32 \pm 25.58	0.5243	1.01 (95% CI=0.99-1.03)
GA	28.73 \pm 2.85	29.23 \pm 2.16	0.5062	0.92 (95% CI=0.73-1.16)
FS days	2.58 \pm 5.46	1.32 \pm 2.53	0.326	1.08 (95% CI=0.92-1.26)
BW	1385.23 \pm 571.85	1345.32 \pm 436.97	0.7901	1.00 (95% CI=0.99-1.01)
RG	11.42 \pm 11.23	7.27 \pm 8.97	0.1693	1.04 (95% CI=0.98-1.11)
V	2.58 \pm 3.73	2.05 \pm 2.89	0.5891	1.05 (95% CI=0.88-1.25)

Table 4: Comparison of The variables.



Analysis of The results and discussion

The first significant datum is the absence of serious events like NEC within the population of preterm infants who were fed exclusively with HM. This is a very important result which is not limited to the population recruited in this study, but confirms the trend of zeroing the incidence of NEC for VLBW and has been already published by the team of the milk bank of "Casa Sollievo della Sofferenza". This is validating that the exclusive use of HM is strongly protective against the NEC. This is well understood if we think about the innumerable bioactive factors composing the OMM, some of which only recently discovered, that bring a defensive action against the inflammation, in addition to exercising a trophic function on the immature intestine favoring maturation and development [26-38,50].

Regarding the intestinal tolerance, the numbers are comforting if we think that the bilious GR and the vomits, which together with other suspect symptoms related to abdominal pathologies (important abdominal distension, blood in the stool) indicate the suspension of enteral feeding, are observed in a percentage <5%. The highest incidence of GR (14%), especially if not bilious, is not symptomatic of food intolerance and it's not an early sign of NEC but of a slower gastric emptying. This is a sign of immaturity that would explain the prevalent share of GRs (about 70%) in the VLBW category [51,52].

In a paper, preterm and LBW infants, feeding with formula compared with donor breast milk, either as a supplement to maternal expressed breast milk or as a sole diet, result in higher risk of developing NEC. Even in our study, the comparison clearly shows that OMM is a life-saving drug. In effect, the exclusive use of OMM in our sample led to the absence and to the minimal incidence of eating disorders and to the non-suspension of feeding. This latest is a fundamental parameter of the assistance-the quick achievement of the exclusive enteral feeding, the subsequent suspension of the parenteral nutrition results in an important reduction of the risk of complications and in a shorter duration of the hospitalization [2-18,24,25,53].

The low incidence of GR during the exclusive feeding with OMM could be explained with a positive action on the gastrointestinal motility, as well as on the overall maturation including the digestion. It should be highlighted the role of the health personnel in encouraging the breast-feeding of preterm infants, reminding mothers of the importance of their milk, and monitoring from the first hours of birth the activation and compliance of the protocol inherent the breast-expressing, since it has proved to be an important strategy for milk production. The psychological support must be taken into account since pulling milk is a way for mothers to overcome the detachment and the psychological drama of a premature birth [54-56].

The comparison between the different kinds of feeding with HM demonstrates that the effect of maximum protection is in part reduced with the DM but remains suitable in improving the tolerance. The lower protective value of the DM is related to its treatment, predominantly involving the pasteurization and the freezing which inactivate or lose part of the immunological heritage and of the enzymes of OMM but overall, many of the positive effects, especially on tolerance, remain [30, 39-41,47-57,66].

The oligosaccharides present in human milk (resistant to pasteurization) have a protective effect from NEC having been shown an inverse correlation between their concentration in milk and the risk of developing this very serious complication, confirming the beneficial action already detected in rats [58,59]. A new pasteurization method is being assessed-a rapid 52-degree process of 5-15 seconds to be used by milk banks that ensures a better preservation of the biological factors of the OMM and that probably will reduce the differences between DM and OMM [60-62].

The precise indication given by the scientific societies and the institutions dealing with child health is to use the DM as alternative to OMM, which remains at the first place in the hierarchy of choices.

However, the result of the statistical comparison between the two kinds of feeding in which no significance was found, confirms their validity. The availability of DM depends on the generosity of the donors who, in a spontaneous and gratuitous way, devote the precious OMM to the Human Milk Banks (HMB). Currently, it is estimated that in Italy the quantity of milk collected in The 38 milk banks and distributed throughout the national territory, can cover only 30% of the needs of the NICUs [63].

The absence of statistical significance between the OMM and the DM in relation to GA and BW shows that even infants of VLBW or ELBW can be fed with their mother's milk. Moreover, in the study population, 60% of VLBW have received OMM. Several stories, even extraordinary, regarded mothers of highly preterm infants inside the BLUD "Allattiamolavita" who succeeded in feeding their children and in donating a part of their milk to the bank [64,65].

The study confirms the importance of the presence of the milk bank as an integral part of the NICU, which worked as supplier of donated HM and as facilitator for the milk production. 6 preterm on 15 (40%) having a BW less than 1000 grams, were fed with their mother's milk, though not always exclusively. We retain that this result deserves attention [66-68]. After all, the ultimate aim of this work is to improve the feeding of preterm infants-an aspect considered fundamental in the care of newborns due to the possible effects on mortality and morbidity in the short and long term [12,9-21,23].

Conclusions

The study highlights the irreplaceability of the OMM in feeding the premature baby, especially if VLBW-it is a real essential drug that helps preventing NEC and food intolerance. It also demonstrates that the DM is a valid substitute if taken before OMM or in case of lack, because it holds the protective capacity against the NEC and the feeding tolerance is not statistically different compared to the OMM. The support to the milk production is interlinked to the donation; the presence of a NICU milk bank promotes the availability of the mother's milk for preterm infants.

Only the dissemination of the culture about the breastfeeding and the milk donation, with the implementation of effective protocols, can lengthen the use of HM, which is a guarantee of better health and well-being for the present and the future of this fragile category of newborns.

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