Clinical Nutrition 38 (2019) 1061–1066

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Meta-analyses

Donor human milk and risk of surgical necrotizing enterocolitis: A meta-analysis

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ARTICLE INFO

Article history:
Received 26 November 2017
Accepted 5 March 2018

Keywords:
Necrotizing enterocolitis
Donor milk
Breastfeeding
Preterm infants

SUMMARY

Background & aim: The prevention of necrotizing enterocolitis (NEC) is a primary goal in the care of preterm and low birth-weight infants. Donor-banked milk (DM)-feeding has been reported to have a protective effect towards NEC with respect to formula-feeding. All the meta-analysis published so far, have been focused on the protective effect of DM on the overall risk of NEC, none of them focused on the risk of the most severe cases on NEC only, that are those requiring surgery. We conducted a meta-analysis of available evidences on the risk of developing surgical cases of NEC in DM-fed preterm and/or low birth weight infants with respect to those formula-fed.

Methods: A search for articles published between January 1960 and January 2018 and addressing the association between DM and surgical NEC was conducted via PubMed, Embase and Cochrane database. We included randomized controlled clinical trials, reporting primary data and involving preterm and/or low birth weight infants fed with preterm formula compared to DM, both as sole diet or complementing own mother's milk. Estimates were pooled using random-effects. Study quality was assessed by GRADE score and risk of bias by the Review Manager software tool.

Results: Four papers were included in the meta-analysis. DM did not exert a beneficial effect of DM on the risk of preventing surgical NEC with respect to formula (RR: 0.45; 95% CI: 0.19–1.09).

Conclusions: This meta-analysis indicates that DM does not exert a clear protective effect, on the surgical cases of NEC with respect to preterm formula. Since DM feeding implies remarkable extra cost for the preparation, storage and delivery of the milk with respect to preterm formula, stronger evidences are required to recommend this type of feeding as a preventive strategy for surgical NEC. Mother's milk, when available, could represents the best choice.

PROSPERO registration number: CRD42015020296

1. Introduction

Prevention of necrotizing enterocolitis (NEC) is one of the most important goals in the day-to-day management of preterm and/or low birth weight neonates [1]. Both direct breastfeeding and own mother's expressed breast milk (EBM) are effective at reducing the risk of NEC, with respect to the formula feeding [2,3]. However, these types of feeding are not always available for a preterm infant, so a promising alternative is the banked donor milk (DM). A Cochrane meta-analysis has concluded that DM-fed preterm and/or low birth weight infants had a 2.77-fold lower risk of developing NEC with respect to formula-fed peers [4]. Two following meta-analysis confirmed this protective role of DM-feeding towards NEC [5,6].

The above-cited papers considered the effect of the feeding on the overall risk of NEC, regardless the clinical severity of the disease. The severity of NEC may widely vary, ranging from mild cases that require a medical treatment only, to life-treating forms, whose treatment is the resection of a portion of the intestine [7].

Abbreviations: CI, confidence interval; DM, donor milk; EBM, expressed breast milk; NEC, necrotizing enterocolitis; NICU, Neonatal Intensive Care Unit; RR, relative risk.

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https://doi.org/10.1016/j.clnu.2018.03.004
0261-5614/

Whether DM-feeding is effective at reducing the risk of the surgical cases of NEC is an essential prerequisite for the correct evaluation of the ratio benefit/cost of DM-feeding, since DM is indeed much more expensive than preterm formula. The consequent evidence that DM prevent the costly surgery for the treatment of the severe NEC cases might be a further motivation for the diffusion of milk banks [8].

Thus, we here perform a meta-analysis of all the available randomized clinical trials that studied the risk of the surgically-treated NEC cases in DM-fed infants, with respect to those formula-fed.

2. Methods

2.1. Search strategy

A systematic search of the literature was carried out in December 2016, April 2017 and January 2018 in the content of MEDLINE via PubMed (www.ncbi.nlm.nih.gov/pubmed), Embase (www.embase.com) and Cochrane database (www.theCochranelibrary.com) following the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group (http://www.prisma-statement.org). We restricted our search to studies in English published between January, 1st 1960 and January, 15th 2018. Letters to the editor, abstracts, and proceedings from scientific meetings were excluded from the analysis. The following search terms were used: ("necrotizing enterocolitis" *OR* "NEC") & (breastfeeding *OR* breastfeeding *OR* breast feeding *OR* breastfed); ("necrotizing enterocolitis" *OR* "NEC") & ("donor milk" *OR* "banked milk" *OR* "donor breast milk"). We excluded the term "surgical" from the search, to avoid missing the papers where this term compared in the tables, only. Two Authors (MS, CA) independently selected the articles and retrieved and assessed the potentially relevant ones. Discrepancies between authors in article selection were resolved by a face-to-face discussion, if the discrepancy stood, a third researcher was consulted (GPM). We also searched for further papers to be included in the analysis by reviewing the bibliographies of all identified relevant papers.

2.2. Inclusion criteria

This search included prospective studies, with a randomized, controlled design (blinded or open), on humans reporting primary data. Studies were included if they involved preterm (<37 gestational weeks) and/or low birth weight (<2500 g) infants fed with preterm formula as sole diet or complemented with own mother's milk compared to DM as sole diet or complemented with own mother's milk.

Outcome measure was the surgically treated NEC. None of the papers included in this study reported the criteria for the surgical treatment of NEC, so we did not establish *a priori* any inclusion criteria for surgical NEC.

2.3. Data collection and extraction

Two of us (MS and CA) screened all study titles and abstracts, and full-text articles of any potentially relevant study were retrieved. The same 2 reviewers assessed articles for eligibility with the use of inclusion criteria. Disagreements were resolved through discussion or adjudicated by a third author (GPM). From each trial the following information were extracted: 1) general characteristics of the studies: first author and year of publication of the article; country; number of the infants enrolled, age and birth weight of the participants; type of feeding (preterm formula, fortified and not fortified DM); inclusion and exclusion criteria; 2) design and characteristics of the data collection; 3) definition of the outcome and 4) main results. Relative risk was considered the main summary measure.

2.4. Study quality and assessment of risk of bias

In order to appraise the quality of the studies included in this review, we used the GRADE score ranging from 0 (minimum) to 4 (maximum) points [9]. This is a systematic and explicit approach to assesses the quality of evidence, based on a score given to each study according to the following parameters: study design, allocation process, follow-up, withdrawals, directness, consistency and effect size. Risk of bias was assessed according to the criteria outlined in the Review manager software 5. This system evaluates seven possible sources of bias: allocation, blinding, incomplete outcome data, selective reporting, and other bias. For each individual domain, we classified studies into low, unclear, and high risk of bias. Review manager software 5 was also used to collect and analyze the data.

2.5. Data analysis

Data analysis was done using Open Meta (analysts) 0.15 software (Brown University, Providence, RI, USA). Crude relative risk (RR) was calculated in the program, thus avoiding biases that may have arisen from adjustments to different confounders of each study. The summary effect was estimated by using random effect models and heterogeneity between the studies was assessed by the chi-square test and quantified by the I^2 statistics, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance.

3. Results

3.1. Studies included in the review

From the systematic search through PubMed, Embase, and Cochrane Library, we retrieved 726 articles. The Cohen's k coefficient for inter-rater reliability was 0.97, indicating excellent agreement among authors. Out of them, 19 articles were potentially considered eligible for inclusion and the full text of those articles were extracted. We excluded 6 systematic reviews or meta-analyses (including 3 Cochrane reviews) [4,10,11]. As well, we excluded 8 original research articles not meeting the inclusion criteria, because of the following reasons (Fig. 1): control group receiving term formula [12], studies comparing the effect of the intake of different percentage of own mother's milk [3,13], study aimed to evaluate the effect of two different fortifiers in DM-fed babies [14], study comparing the protective effect of EBM vs preterm formula towards the development of NEC [2], observational design [15] no control group receiving formula [16] and finally, study not reporting the type of NEC treatment [17]. We also excluded the paper by Lucas et al. [18], although this paper fulfilled the inclusion criteria, since this study was published back in 1984 and conducted even earlier, when the preterm infants were relatively large by today's "standards" and the neonatal practices were very different from nowadays. So, two articles were included directly in the analysis [19,20]. At this point, we left out from the meta-analysis two recent papers whose robust design was within our inclusion criteria, but they did not report explicitly the number of surgical NEC cases [21,22]. We considered surgical NEC cases in the series of the study by O'Connor et al. [21], those infants with NEC stage $\geq$ II according to Bell classification, since the criteria for classification in stage $\geq$ II are surgery indications, as stated by the same Authors in the methods section of the paper: "radiographic, ultra-sound, or surgical evidence of pneumatosis, gas in the portal

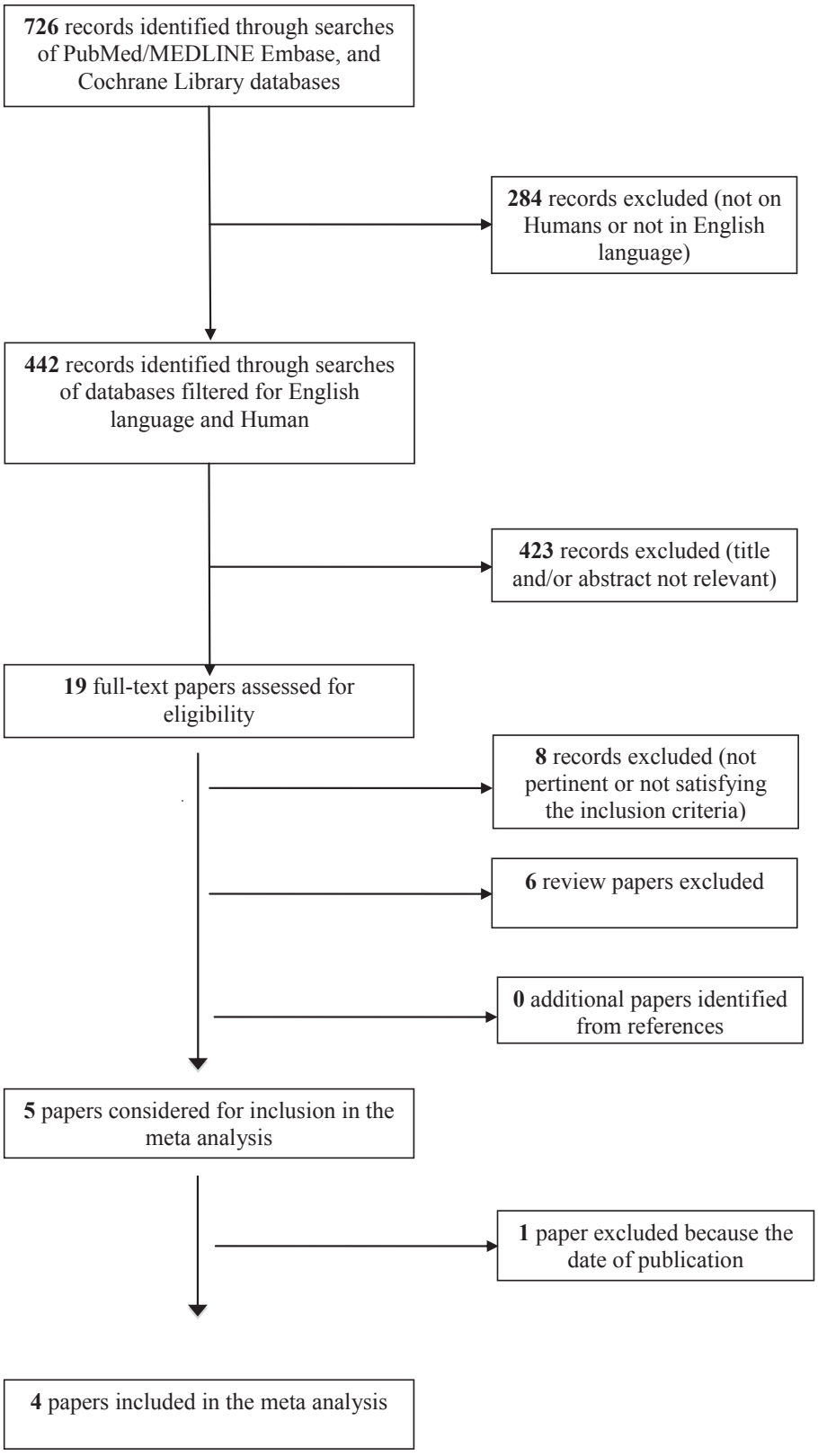

Fig. 1. Flowchart of the study selection process.

tract, or perforation or histological evidence of bowel ischemia". Regarding the paper by Schanler et al., we contacted directly the corresponding Author by e-mail, asking how many surgical NEC cases were in the cohorts described in the paper published in 2005 [22]. So, we included four papers in the meta-analysis (Fig. 1). The main characteristics of these studies and results of quality assessment are provided in Table 1. Table 2 provide details about the bias risk.

Table 1
Characteristics of the studies, whose design fulfilled the criteria for inclusion in the meta-analysis. The two studies described in the paper by Lucas et al. were not included in the meta-analysis, since they were published in 1984.

Reference	n of infants enrolled intervention	Baseline data	Study design	NEC primary or secondary outcome	Quality score
Lucas, A 1984 [18]	83 not fortified DM only/76 preterm formula only		randomized, controlled	secondary	2
Lucas, B 1984 [18]	170 not fortified DM only/173 preterm formula only		randomized, controlled	secondary	2
Schanler, 2005 [22]	81 MM and pasteurized DM/92 MM and preterm formula	gest age = 27 ± 2 vs 27 ± 2 wk bw = 983 ± 207 vs 996 ± 152 g	blinded, randomized, controlled	primary	3
Cristofalo, 2013 [19]	29 fortified DM only/24 preterm formula only	gest age = 27.5 ± 2.4 vs 27.7 ± 2.5 wk bw = 983 ± 207 vs 996 ± 152 g	multicenter blinded, randomized, controlled	primary	3
Corpeleijn, 2016 [20]	183 DM with 89% of total enteral intake by own MM/190 preterm formula with 84% of total enteral intake by own MM	gest age = 28 ± 2.3 vs 28.6 ± 2.3 wk bw = 1065 (830–1265) vs 1077 (854–1275) g	double-blinded, randomized, controlled	secondary	4
O'Connor, 2016 [21]	181 DM only/182 preterm formula only	gest age = 27.5 ± 2.4 vs 27.8 ± 2.7 wk bw = 995 ± 273 vs 996 ± 272 g	double-blinded, randomized, controlled	secondary	4

DM = donor milk; MM = mother milk; Lucas A: DM vs preterm formula only; Lucas B: DM vs preterm formula both supplemented with own mother's breastmilk.

Table 2
Risk of bias of the studies included in the meta-analysis.

Reference	Allocation (selection bias)	Blinding (performance and detection bias)	Incomplete outcome bias (attrition bias)	Selective reporting (reporting bias)	Other source of bias	Bias score
Schanler, 2005 [22]	no	present	unclear	no	no	low
Cristofalo, 2013 [19]	no	present	no	no	no	low
Corpeleijn, 2016 [20]	no	present	no	no	no	low
O'Connor, 2016 [21]	no	present	no	no	no	low

3.2. Risk of NEC

In the meta-analysis, we included all the RCTs listed in Table 1, unless the paper by Lucas. When the data from the trials were pooled with a random effect model, no preventive effect of DM on the risk of surgical NEC was found, narrowly not significant (RR: 0.45; 95% CI: 0.19–1.09). No heterogeneity between studies was detected (p = 0.54) (Fig. 2). Interestingly, only one of the studies reported a statistically convincing protective effect of DM towards NEC [20]. Out of the 4 papers selected, two got the highest GRADE score of 4 and the other two scored 2.

4. Discussion

This meta-analysis investigated the effect of DM with respect to preterm formula on the risk of surgery – requiring cases of NEC in low birth-weight and preterm babies and showed that although a relative risk reduction of roughly 50% was found in DM-fed infants, the difference did not reach statistical significance.

Five previous meta-analyses have been published on the effect of DM-feeding on the overall risk of NEC. Three meta-analysis by the Cochrane group issued in 2001, 2007 and 2014, and other two studies published in 2003 and 2007, respectively [4–6,10,11]. All these previous meta-analysis found a protective effect of DM on risk of overall NEC onset; in particular the most recent Cochrane review reported a 2.7-fold effect. None of these papers considered the surgical NEC only.

In the most severe form, NEC is a life-threatening condition, characterized by a full thickness necrosis and perforation of the intestinal lining. It is likely that the immune-enhancing molecules of DM, whose presence is reduced by the pasteurization, are able to limit the inflammation of the mild form of NEC, those requiring a medical treatment only, but are not sufficient to keep under control the massive inflammatory necrosis of the intestinal wall, once it develops. On the contrary, a direct detrimental effect of cow's milk protein on the intestinal mucosa has been ruled out by recent studies [19,22]. This finding is important, since it implies that a complete human milk diet is not a efficient strategy to prevent NEC.

One limitation of this analysis is the small number of the studies considered. Out of the 440 papers identified and 19 assessed for eligibility, only 4 were eligible for inclusion. This reflects the difficulty to conduct these trials in a critical setting, such as NICUs. In addition, the randomization of infants to formula and DM-feeding is not possible for ethical reasons, when EBM or direct

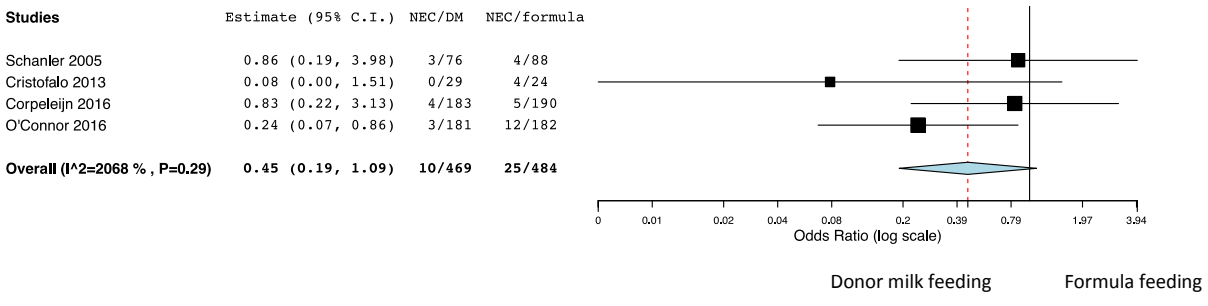

Fig. 2. Forest plot for the relative risk pooling the results of all studies included in the meta-analysis; DM = donor milk.

breastfeeding is available or is possible its promotion. At the moment, there are not RCTs studying the effects of DM-feeding on any pre-term health outcome at clinicaltrials.gov.

In addition, one of the two largest studies we found on Pubmed, the one by Lucas et al. [18], was published 33 years ago and was obviously conducted over years earlier than that. At that time, the preterm infants were relatively large by today's "standards" and the neonatal care was not as developed as today. Before the '90, oxygen delivery to gut mucosa was impaired by the lack of available means to rapidly improve lung functional maturation (surfactant administration) and the techniques of early feeding were not so advanced [23,24]. Thus, the impact of the type of feeding was definitely more important in the prevention of NEC, with respect to the weight that might have nowadays. For those reason, this paper was excluded from the meta-analysis, although it fulfilled all the inclusion criteria.

It also should be considered the heterogeneity of the interventions and of the low quality score of the studies included. Two studies compared the effect of DM-feeding as sole diet versus preterm formula as sole diet. In Early Nutrition study, the Authors compared the effect of full enteral feeding with DM and formula feeding, both largely complemented by own mother's milk by 10 days of age, at which time all infants received bovine milk fortifiers. However, considering that many cases of NEC develop after 10 days of life, i.e. out of the intervention period of the study, their data cannot thoroughly assess the effect of donor milk in the prevention of NEC [20]. The GRADE score of the studies included ranges from 1 to 4, with two studies obtaining the highest. In addition, one study with the highest available GRADE score, is the one that raises concerns about the duration of the intervention [21,22]. The occurrence of NEC was a primary outcome in two protocols only, out of the four considered [19,22]. Finally, in this meta-analysis, we have considered the occurrence of NEC as a separated outcome. Since other negative conditions, such as infectious diseases, might worsen and/or complicate the clinical course of preterm/low birth weight babies, the NEC occurrence should have been adjusted for the other causes of morbidity and mortality. However, this was not possible in consideration of the primary data available.

Although not specifically related to this meta-analysis, one should consider also the risk of language and publication bias. While it is likely that the first might not weight so much since all the relevant papers are now published in English, the second might have a role, since the RCTs with positive results are more prone to be accepted for publication.

In Italy, there are at present 28 fully active milk banks that provide roughly 9500 L of milk per year [25]. A premature/low birth weight infant, during a mean length of stay in Neonatal Intensive Care Unit (NICU) of approximately 60 days, is expected to receive 12 L of DM. In Italy a liter of DM has been estimated to have a mean cost of 70–110 €, the DM feeding of a baby costs 840–1300 € [26].

Within our economic context, the efficacy of the health interventions should be endorsed by solid scientific evidences and a rigorous evaluation of the cost and benefits of interventions. Assuming that the alternative of DM is the preterm formula costing 240 € (for a cost of 20 € per a liter), the extra-cost per DM-fed infant would be 600–1060 € [27]. In the lack of evidences of a preventive effect of DM towards NEC, the question is whether the extra-cost for DM-feeding of preterm babies is worthy or it is preferable to invest this money for facilitating the access to the NICUs to the breastfeeding mothers and for developing more effective treatments for the cases of NEC, that require surgery.

The safety of DM is not a matter of concern, nowadays. The milk collection procedures, although are not standardized across the different Countries, allow having germ – free samples. Also, the chemical and clinical hazard, such as donor smoking and alcohol consumption, are usually considered upon donation. The main problem related to DM feeding is the nutritional value of the milk, in particular, the protein content. DM undergoes pasteurization process and freeze–thaw cycles before storing and these procedures alter the protein structure and function [28,29].

Direct breast milk and/or EBM, when available, are the optimal choice for the feeding of the preterm/low birth weight infants, offering the optimal and more balanced nutritional pattern and the highest and evidence-based protection towards NEC. Moreover, they do not add costs to the healthcare system. So efforts of the health authorities should convincingly be focused on facilitating both the access of mothers into the NICUs and supporting these feeding practices.

Disclaimer

None.

Source of support

The study was performed with departmental funding.

Conflict of interest

None to be declared.

Acknowledgment

The Authors would like to thank Prof. Richard J. Schanler, for kindly sharing the data about the surgical NEC in the series described in his paper.

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