Impact of standardised feeding regimens on incidence of neonatal necrotising enterocolitis: a systematic review and meta-analysis of observational studies

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CRD summary
This review assessed the effects of standardised feeding regimens (SFR) on necrotising enterocolitis (NEC) in pre-term, low birth weight newborns. The authors concluded that SFR may be the most important tool in preventing or minimising NEC, but randomised controlled trials are required. These conclusions reflect limited evidence from a small number of observational studies; the recommendation for more robust research appears appropriate.

Authors' objectives
To assess the effects on necrotising enterocolitis (NEC) of standardised feeding regimens (SFR) in pre-term, low birth weight (LBW) infants.

Searching
The Cochrane CENTRAL Register (Issue 4, 2002), MEDLINE, EMBASE, CINAHL and the Proceedings of the Pediatric Academic Societies (published in Pediatric Research from 1980) were searched in October 2003 for reports in any language; the search terms were reported. Reference lists of identified observational studies and personal files were screened.

Study selection
Study designs of evaluations included in the review
Observational studies reporting data before and after the SFR were eligible for inclusion.

Specific interventions included in the review
Studies that examined the implementation of an SFR were eligible for inclusion. The studies had to report well-documented guidelines for enteral feeding. The included studies used a variety of SFRs with different starting dates or clinical conditions for feeding, different types of feed (breast milk, formula, sterile water followed by formula, and diluted formula), and different volumes at the start and different incremental volumes (full details were reported).

Participants included in the review
Studies of pre-term, LBW neonates were eligible for inclusion; LBW was defined as less than 2,500 g. Studies included LBW neonates, very LBW neonates (not defined) and neonates weighing less than 2 kg.

Outcomes assessed in the review
Studies that reported the incidence of definite, or stage II or higher, NEC were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors stated that they did not assess validity.

Data extraction
Two reviewers independently extracted the data and resolved any disagreements through discussion. For each study, details of the SFR and the number of neonates with NEC were extracted before and after the introduction of the SFR to calculate the risk ratio (RR) with 95% confidence intervals (CIs). The authors of the primary studies were contacted for
clarification of data or additional data.

**Methods of synthesis**

**How were the studies combined?**
The RRs were pooled using a random-effects model.

**How were differences between studies investigated?**
 Statistical heterogeneity was assessed (test not reported) and forest plots were presented. The meta-analysis was repeated after excluding the study reporting the highest reduction in NEC with an SFR. A fixed-effect meta-analysis that also excluded this study was conducted. A pre-planned subgroup analysis that included only very LBW neonates was also conducted.

**Results of the review**

Six before-and-after studies (n approximately 8,500) were included.

The SFR was associated with a statistically significant reduction in the incidence of NEC (RR 0.13, 95% CI: 0.03, 0.50). Statistically significant heterogeneity was found (P<0.001). All studies reported a reduced incidence of NEC after the adoption of an SFR.

There was a reduction in NEC incidence associated with SFRs in very LBW neonates, but it was not statistically significant (RR 0.57m 95% CI: 0.31, 1.06, P=0.08, based on 4 studies). Statistically significant heterogeneity was found (P=0.02).

After excluding the study reporting the highest reduction in NEC, no statistically significant heterogeneity was found (P=0.8) and the reduction in NEC with an SFR in very LBW neonates was statistically significant (RR 0.71, 95% CI: 0.52, 0.97, P=0.03). The result was similar when using a fixed-effect model.

**Authors’ conclusions**

SFRs may be the most important tool in preventing or minimising NEC in pre-term neonates, but randomised controlled trials (RCTs) are required.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. It was unclear why inclusion was restricted to observational studies. Several relevant sources were searched and attempts were made to reduce language bias. The authors appeared to make little attempt to identify unpublished studies. Methods were used to minimise reviewer errors and bias in the extraction of data, but it was not clear whether similar steps were taken at the study selection stage. Validity was not assessed, so the reliability of the results cannot be assured.

Adequate details of the feeding regimens used in the included studies were provided, but not other study details. Statistical heterogeneity was assessed. Owing to the considerable statistical and clinical heterogeneity, the pooled results may not be reliable. Having found statistically significant heterogeneity, sensitivity analyses were performed but these did not alter the conclusions. There was general discussion about the potential sources of differences among the studies, including changes in practice over the 25-year time period of the included studies. The authors’ conclusions reflect limited evidence from a small number of observational studies; their recommendation for more robust research appear appropriate.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that RCTs of SFRs are justified but may be difficult to conduct in centres that have...
already introduced SFRs. They also stated that there is a need to examine factors associated with reductions in the risk of NEC, such as patient characteristics and specific guidelines directed at enteral feeding in neonates with risk factors (including haemodynamically significant patent ductus arteriosus and/or sepsis and bile-stained gastric aspirates).

Bibliographic details

PubMedID
15724039

DOI
10.1136/adc.2004.059741

Original Paper URL
http://fn.bmj.com/content/90/2/F147.full

Indexing Status
Subject indexing assigned by NLM

MeSH
Enterocolitis, Necrotizing /epidemiology /prevention & control; Feeding Methods; Humans; Infant Formula; Infant Nutritional Physiological Phenomena; Infant, Low Birth Weight; Infant, Newborn; Infant, Premature, Diseases /prevention & control; Infant, Very Low Birth Weight; Intubation, Gastrointestinal /methods; Milk, Human; Risk Factors

AccessionNumber
12005009466

Date bibliographic record published
28/02/2007

Date abstract record published
28/02/2007

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.