Banked preterm versus banked term human milk to promote growth and development in very low birth weight infants (Review)

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[Intervention Review]

Banked preterm versus banked term human milk to promote growth and development in very low birth weight infants

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ABSTRACT

Background

Human milk banking has been available in many countries for the last three decades. The milk provided from milk banking is predominantly term breast milk, but some milk banks provide preterm breast milk. There are a number of differences between donor term and donor preterm human milk.

Objectives

To determine the effect of banked preterm milk compared with banked term milk regarding growth and developmental outcome in very low birth weight infants (infants weighing less than 1500 g).

Search strategy

We used the standard methods of the Cochrane Neonatal Review Group, including a search of the Cochrane Neonatal Group specialized register and the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, January 2010). We searched the computerised bibliographic databases MEDLINE (1966 to February 2010), EMBASE (1988 to February 2010) and Web of Science (1975 to February 2010). We searched reference lists of all selected articles, review articles and the Oxford Database of Perinatal Trials. We also searched abstracts from neonatal and pediatric meetings (PAS electronic version from 2000 to 2009, ESPR hand search from 2000 to 2009). We applied no language restrictions.

Selection criteria

Randomised and quasi-randomised trials comparing banked donor preterm milk with banked donor term milk regarding growth and developmental outcomes in very low birth weight infants

Data collection and analysis

We planned to perform assessment of methodology regarding blinding of randomisation, intervention and outcome measurements as well as completeness of follow-up. We planned to evaluate treatment effect using a fixed-effect model using relative risk (RR), relative risk reduction, risk difference (RD) and number needed to treat (NNT) for categorical data and using mean, standard deviation and weighted mean difference (WMD) for continuous data. We planned an evaluation of heterogeneity.

Main results

No studies met the inclusion criteria.

Authors' conclusions

There are no randomised trials that compare preterm banked milk to banked term milk to promote growth and development in very low birth weight infants.

PLAIN LANGUAGE SUMMARY

Banked preterm versus banked term human milk to promote growth and development in very low birth weight infants

Donor expressed milk processed by human milk banks has been used to provide preterm infants with breast milk when there are circumstances that preclude the use of mother's own milk. Preterm milk differs significantly from term breast milk. We were unable to identify any studies that compared donor preterm milk with donor term milk to promote growth and development in very low birth weight infants.

BACKGROUND

Description of the condition

Breast milk is the milk of choice when feeding the preterm very low birth weight infant. Human milk provides a variety of benefits compared to formula. In preterm infants, reported benefits include faster gastric emptying (Cavell 1981; Ewer 1994), faster attainment of full enteral feeding (Uraizee 1989; Lucas 1990), enhanced stimulation of gastrointestinal motility and improved intestinal growth and maturation (Sheard 1988; Groer 1996). Breast milk is associated with a reduction in the incidence of necrotising enterocolitis and late onset sepsis (Narayanan 1984; Schanler 1999). Preterm infants fed human milk appear to have improved neurodevelopmental outcome compared with infants fed formula milk (Anderson 1999). This association has been supported in the extremely low birth weight (ELBW) infant (Vohr 2006). Neonates fed breast milk tend to have improved visual development with less retinopathy of prematurity (Hylander 1995). However, there are circumstances when mother's breast milk may not be available. These circumstances occur when mothers cannot provide their own milk due to maternal illness, inability to produce breast milk or due to concerns regarding certain prescription medications.

Description of the intervention

Human milk banking has been available in many countries for the last three decades and has played an important role in neonatal care. There are a number of donor milk banks in North America, United Kingdom, Europe and Australia. Human milk is donated to the milk bank voluntarily. Donors are screened for HIV, Hepatitis B and C, HTLV and syphilis. The screening, processing and shipping of donor breast milk incur considerable costs. The cost per ounce of expressed milk supplied to institutions varies from country to country. In the United States the estimated cost is USD 3 per ounce; in the UK it is GBP 3 per ounce including processing and shipping costs (Arnold 2002).

Donor expressed milk has been used to provide preterm infants with breast milk when circumstances otherwise preclude the use of mother's own milk. Exclusive feeding with donor breast milk has been shown to reduce the incidence of necrotising enterocolitis when compared to formula (McGuire 2003; Boyd 2006), but growth was slower. This benefit was only seen when breast milk was the sole dietary source. Some studies using donor banked milk or formula as a supplement to mother's own milk did not find any significant differences in reduction of necrotising enterocolitis (Lucas 1984; Schanler 2005). There appears to be no evidence supporting enhanced long term outcome in infants fed donor milk (Modi 2006).

How the intervention might work

The milk provided from milk banking is predominantly term breast milk (often produced later in lactation so it has a different nutrient content), although many breast milk banking services now also batch and provide donated preterm breast milk (Tully 2001; Wight 2001). There are a number of differences be-

tween term and preterm human milk. The nutritional and non-nutritional components of human milk differ as gestational age advances. The relative constituents of protein, fat and carbohydrate differ (Gross 1980; Butte 1984) as do the non-nutritional components including variations in digestive hormones, growth factors, immunological factors, vitamins, minerals and trace elements (Schanler 1980; Saarela 2005). Long chain polyunsaturated fatty acids (LCPUFA) found in both term and preterm milk may differ. LCPUFA play an important role in optimal brain development and retinal maturation (Genzel-Boroviczeny 1997). Donor breast milk undergoes a number of different processes including freezing and pasteurisation. These processes alter the nutritional composition of the milk and may affect preterm donor milk in a different way to term donor milk. Pasteurisation affects nutritional components resulting in slightly slower growth of infants on donor breast milk compared to raw unpasteurised human milk (Stein 1986). Pasteurisation affects immunological factors resulting in lower levels of lactoferrin and IgG. It eliminates white blood cells and bacteria. Despite pasteurisation IgA, bifid growth factor and lysozyme remain intact (Ford 1977). Holder pasteurisations (62.5 degrees of Celsius for 30 minutes) seems to be superior to heat treatment at 56 degrees of Celsius for 30 minutes in terms of CMV elimination (Evans 1978). Freezing will eliminate most of the viruses and does not appear to influence nutritional quality of the milk (Wight 2001). Freezing does reduce the concentration of lysozyme by up to 20%, and also destroys all white blood cells. Microwaving affects the milk in the same way as described with pasteurisation (Quan 1992).

Why it is important to do this review

The inherent nutritional and non-nutritional components of preterm and term donor milk differ and the effects of freezing and pasteurisation may alter the composition of preterm and term donor milk differently. Therefore, the effect of banked donor preterm milk compared to donor term milk in the very low birthweight infant warrants further investigation.

OBJECTIVES

To determine the effect of banked donor preterm milk compared with banked donor term milk regarding growth and developmental outcomes in very low birth weight infants (infants weighing less than 1500 g).

The following comparisons were planned:

Any banked donor preterm milk (with or without fortification) versus any banked donor term milk (with or without fortification)

The following subgroups were planned:

1. Banked preterm milk with fortification (using multicomponent breast milk fortifier) versus banked term milk with fortification (using multicomponent breast milk fortifier);

2. Banked preterm milk without fortification versus banked term milk without fortification.

Banked donor preterm milk (with or without fortification) versus banked donor term milk (with or without fortification) where both were used as sole enteral diet

The following subgroups were planned:

1. Banked donor preterm milk with fortification versus any banked donor term milk with fortification where both were used as sole enteral diet;

2. Any banked donor preterm milk without fortification versus any banked donor term milk without fortification where both were used as sole enteral diet.

Any banked donor preterm milk (with or without fortification) versus any banked donor term milk (with or without fortification) in the extremely low birth weight infant

The following subgroups were planned:

1. Any banked donor preterm milk with fortification versus any banked donor term milk with fortification in the extremely low birth weight infant;

2. Any banked donor preterm milk without fortification versus any banked donor term milk without fortification in the extremely low birth weight infant.

METHODS

Criteria for considering studies for this review

Types of studies

Trials using randomisation or quasi-randomisation of patients were eligible for inclusion. Published or unpublished studies were eligible for inclusion. Unpublished studies or studies published only as abstracts would be included if assessment of study quality was possible and if other criteria for inclusion were fulfilled.

Types of participants

Very low birth weight infants (infants weighing less than 1500 g) fed donor banked human milk. Infants receiving partial enteral feeding (formula or mother's own milk) at study entry were eligible.

Types of interventions

Use of banked donor preterm milk versus banked donor term milk with or without fortification fed either as a sole enteral diet or as a supplement to mother's own milk.

Types of outcome measures

Primary outcomes

1. Short-term growth parameters: time to regain birth weight (days of life), weight gain (grams/day), length gain (centimetres/week), head growth (centimetres/week) at discharge;
2. Longer-term growth parameters (following discharge from hospital): weight gain (grams/week), length gain (centimetres/week), head growth (centimetres/week) at four month follow-up;
3. Neurodevelopmental outcomes at term corrected and at 18 to 24 months using validated assessment tools.

Secondary outcomes

1. Incidence of necrotising enterocolitis (defined as Bell's Stage 2 or greater);
2. Incidence of late onset sepsis;
3. Duration of total parenteral nutrition use (days);
4. Time to full enteral feeds (days);
5. Feeding intolerance defined as abdominal distension with large gastric residuals (> 50% of previous feed).

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Review Group.

Electronic searches

Electronic searches included a search of the Cochrane Neonatal Group specialized register and the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, January 2010). We identified relevant studies by searching the following: (1) computerised bibliographic databases: MEDLINE (1966 to February 2010), EMBASE (1988 to February 2010) and Web of Science (1975 to February 2010); (2) the Oxford Database of Perinatal Trials. The electronic search included the following keywords "donor expressed milk", "banked expressed milk" and MeSH search terms "Infant, Newborn" AND "Milk, Human" AND "Milk Banks". We limited trials to clinical trials where 'limits' option was available. We applied no language restrictions.

Searching other resources

Other searches included reference lists of all selected articles as well as review articles. We also searched unpublished, in press and in progress trials and abstracts from neonatal and pediatric meetings (PAS electronic version from 2000 to 2009, ESPR hand search from 2000 to 2009).

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group.

Selection of studies

Each review author independently searched for trials and selected studies for inclusion with comparison and resolution of any differences.

Data extraction and management

If eligible trials were identified, each review author planned to independently extract the data and compare results. We planned to resolve any disagreements through discussion.

Assessment of risk of bias in included studies

Each review author planned to independently assess the methodology of included trials and resolve any differences through discussion. If trials were eligible, we planned to assess the studies with regard to blinding of randomisation, intervention and outcome measurements as well as completeness of follow-up. If available, we planned to add these data to the table 'Characteristics of Included Studies'.

In addition, we planned to evaluate the following methodological issues and enter the information in the Risk of Bias table:

1. Sequence generation: Was the allocation sequence adequately generated?
2. Allocation concealment: Was allocation adequately concealed?
3. Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?
4. Incomplete outcome data: Were incomplete outcome data adequately addressed?
5. Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?
6. Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?

Measures of treatment effect

We planned to evaluate categorical data by calculating the relative risk (RR), relative risk reduction, risk difference (RD) and number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH). Mean and standard deviation were to be obtained for continuous data and analysis performed using the weighted mean difference (WMD). For each measure of effect, we planned to calculate the 95% confidence interval.

Assessment of heterogeneity

We planned to examine heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. If we detected statistical heterogeneity, we planned to explore the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments) using *post hoc* subgroup analyses.

Data synthesis

If multiple studies were identified and meta-analysis was judged to be appropriate, the analysis would have been performed using Review Manager software (RevMan 5, The Cochrane Collaboration). For estimates of typical relative risk and risk difference, we planned to use the Mantel-Haenszel method. For measured quantities, we planned to use the inverse variance method. All meta-analyses were to be done using the fixed-effect model.

Subgroup analysis and investigation of heterogeneity

The primary objective was to compare any banked preterm donor milk (with or without fortification) to any banked term donor milk (with or without fortification).
Subgroup comparisons of preterm donor milk with fortification to banked term donor milk with fortification and finally preterm donor milk without fortification to banked term donor milk without fortification were planned.

RESULTS

Description of studies

See: Characteristics of excluded studies.
See Characteristics of Excluded Studies table.
The initial search identified 64 abstracts. Of these, we identified six as potentially relevant. However, none met the inclusion criteria for this review. A number of studies compared donor breast milk with formula (Gross 1983; Tyson 1983; Lucas 1990; Schanler 2005) and some of these were the subject of a systematic review (McGuire 2003), but none compared donor preterm milk with donor term milk. One study (Stein 1986) compared pooled pasteurised breast milk with untreated mother's own milk but did not compare donor preterm milk with donor term milk.

Risk of bias in included studies

No studies met the inclusion criteria.

Effects of interventions

No studies met the inclusion criteria.

DISCUSSION

We found no randomised controlled trials comparing preterm banked breast milk with banked term breast milk in the very low birth weight infant; therefore, this systematic review did not establish whether preterm donor milk conferred any health benefits compared to term donor milk fed solely or as part of the overall enteral diet of the very low birth weight infant.

Previous studies have highlighted the benefits of donor expressed breast milk compared to formula. Each of these studies used pooled pasteurised breast milk, a combination of both preterm and term donor milk and so it is not possible to determine whether preterm donor milk had a greater influence on outcome compared with term donor milk. It is biologically plausible that preterm donor may confer additional benefits to the preterm infant compared to term donor milk because the nutritional components differ. The non-nutritional components also differ, including variations in digestive hormones, growth factors, immunological factors, vitamins, minerals and trace elements, all of which may contribute to improved well-being in the preterm infant. However, it is unlikely that there would be any future randomised controlled trials comparing preterm donor milk with term donor milk, where each is the sole agent used. Reasons may include the limited supply of preterm donor milk, either because of limited donated volumes or limited numbers of breast milk banks that supply preterm breast milk. However, future randomised controlled trials could be performed comparing preterm with term banked breast milk as an adjunct to mother's own milk (where the maternal supply may be not be sufficient to keep up with the demand) or formula feeding in the very low birth weight infant.

AUTHORS' CONCLUSIONS

Implications for practice

We found no randomised controlled trials that compared banked preterm milk versus banked term milk to promote growth and development in very low birth weight infants.

Implications for research

Although it is biologically plausible that banked preterm milk may be more suitable than banked term milk in feeding the preterm infant, it is unlikely that there would be any future randomised controlled trials comparing either milk source as a sole agent. However, future randomised controlled trials could be performed comparing banked preterm milk to banked term milk as an adjunct to mother's own milk or formula feeding.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Gross 1983	This study compared human milk with formula.
Quigley 2007	This was a systematic review of donor breast milk compared to formula.
Schanler 2005	This study compared donor human milk versus preterm formula as an adjunct to mother's own milk.
Stein 1986	This study compared pooled pasteurised breast milk with that of untreated mother's own milk.
Tyson 1983	This trial compared pooled bank milk with enriched formula.

DATA AND ANALYSES

This review has no analyses.

HISTORY

Protocol first published: Issue 1, 2009

Review first published: Issue 6, 2010

CONTRIBUTIONS OF AUTHORS

Dr. Dempsey conceived and designed the review.

Both review authors performed separate data collection for the review.

DECLARATIONS OF INTEREST

None

INDEX TERMS

Medical Subject Headings (MeSH)

*Child Development; *Milk Banks; *Milk, Human [chemistry]; Infant, Newborn; Infant, Very Low Birth Weight [*growth & development]

MeSH check words

Humans