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Re-feeding versus discarding gastric residuals to improve growth in preterm infants (Protocol)

Abiramalatha T, Thanigainathan S, Balakrishnan U

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[Intervention Protocol]

Re-feeding versus discarding gastric residuals to improve growth in preterm infants

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy and safety of re-feeding compared to discarding gastric residuals to improve growth in preterm infants. The allocation should have been started in the first week of life and should have been continued at least until the baby reaches full enteral feeds. The investigator could choose to discard the gastric residual in the re-feeding group, if the gastric residual quality is not satisfactory. However, the criteria for discarding gastric residual should have been pre-defined.

We will undertake subgroup analysis based on the gestational age (≤ 27 weeks, 28 weeks to 31 weeks, ≥ 32 weeks), birth weight (< 1000 g, 1000 g to 1499 g, ≥ 1500 g), type of milk (human milk or formula milk), quality of the gastric residual (fresh milk, curded milk or bile-stained gastric residual), the volume of gastric residual replaced (total volume, 50% of the volume, volume of the next feed or pre-specified volume irrespective of the volume of the aspirate, e.g. 2 mL, 3 mL, etc.), and whether the volume of gastric residual that is re-fed is included in or excluded from the volume of the next feed (Subgroup analysis and investigation of heterogeneity).

BACKGROUND

Description of the condition

Providing adequate nutrition is a key component of the health care of preterm neonates. There is increasing emphasis on early initiation and appropriate advancement of enteral feeds with the aim of achieving full volume enteral feeds at the earliest opportunity (Dutta 2015; Stevens 2016). The major hindrance to advancing feed volumes in preterm infants is feed intolerance and the risk of necrotising enterocolitis (NEC).

Feed intolerance is a common problem in preterm infants. It causes frequent interruption and delayed advancement of enteral feeds resulting in protracted use of total parenteral nutrition (TPN) and central venous lines (CVL), increasing their complication rate (Hermansen 2005; Duro 2011; Kaur 2015). Delay in establishing full enteral feeds is a significant contributor to growth failure in preterm infants, resulting in neurodevelopmental impairment and long-term metabolic complications (Franz 2009; Embleton 2013; Stevens 2016).

Gastric residual is the measure of volume of milk along with gastrointestinal secretions remaining in the stomach after a certain time

interval. Routine monitoring of gastric residual (volume and/or colour) in preterm infants on gavage feeds is a common practice in many neonatal intensive care units (NICUs), and is used to guide the initiation and advancement of gavage feeds (Gregory 2012). An increase in, or an altered gastric residual are considered as signs of feed intolerance, or an early sign of NEC (Li 2014). Increased gastric residual is common in preterm infants, due to many intrinsic and extrinsic factors. The intrinsic factors are related to the inherent immaturity of the gastro-intestinal system in the form of delayed gastric emptying, slower intestinal transit, inadequate secretion of gut hormones and enzymes and possible duodeno-gastric reflux (Ittmann 1992; Riezzo 2000). The extrinsic factors are use of formula feeds, certain drugs such as theophyllines, mydriatics and opioids and sickness of the baby, which delay gastric emptying (Li 2014).

Description of the intervention

The decision on whether to re-feed or discard gastric residual in preterm infants is generally made based on the unit protocol, physician's advice or the nurse's experience. A small survey of neonatal nurses found that only 4% consistently replaced gastric residual after aspiration (Hodges 1993). The results of adult studies are controversial. While one study shows a decrease in the incidence and severity of delayed gastric emptying episodes with re-feeding gastric residual (Juvé-Udina 2009), the other study shows an increase in complications such as tube clogging, diarrhoea and nausea (Booker 2000).

In newborn infants, there are expert suggestions on the management of gastric residual based on its quantity and quality. Dutta and colleagues suggested re-feeding 50% of gastric residual or 5 mL/kg, whichever is higher and others suggest replacing fresh or curded milk and bile-stained aspirates, but not hemorrhagic gastric residual (Dutta 2015; Salas 2015). However, Salas and colleagues showed that replacing gastric residual did not decrease the time to reach full enteral feeds or increase the incidence of NEC in preterm infants (Salas 2015).

How the intervention might work

Gastric residual contains milk/partially digested milk and gastric secretions composed of gastric acid, enzymes, hormones and trophic substances that aid in digestion and promote gastro-intestinal motility and maturation, discarding of which may have negative influence on the infant's gastro-intestinal system (Juvé-Udina 2009; Williams 2010; Li 2014; Parker 2015). Discarding the partially digested milk and feeding the baby with fresh milk may increase the stress on the preterm gut, increasing the risk of feed intolerance.

Gastric acid facilitates protein and lipid digestion. Activation of pepsinogen to pepsin and protein hydrolysis requires an acidic environment with a pH < 4 (Neu 2007). Gastric lipase plays an important role in lipid digestion (Neu 2007). Lingual lipase from saliva commences to act in the acidic environment of the stomach. Gastric acid, as it enters the duodenum, promotes the secretion of bile and pancreatic enzymes. Thus, discarding the gastric acid may adversely influence the digestive capacity of the preterm gut. The gastric secretions contain sodium, potassium and chloride ions, discarding which, may result in deficiency of these ions. Gastric mucin that is protective to the mucosa and regulatory peptides such as leptin and ghrelin are also lost in the discarded gastric residual.

Moreover, the acidic environment in the stomach acts as a barrier for bacterial growth and entry into the lower gastro-intestinal tract. This is shown in studies on H2 blockers, which cause bacterial overgrowth in the distal intestine and increase the incidence of NEC and nosocomial sepsis (Graham 2006; Guillet 2006). Manually removing the gastric acid every two to three hours may create an alkaline environment and increase the risk of NEC and late-onset sepsis.

However, re-feeding bile- or blood-stained gastric residual might result in gastric irritation and emesis, worsening feed intolerance (Salas 2015). Returning the gastric contents after manipulation might increase the risk of infection of the preterm gut, resulting in NEC and/or sepsis (Booker 2000).

Why it is important to do this review

Given the potential benefits of re-feeding gastric residual as well the possible risks associated with re-feeding, we will undertake a systematic review that identifies and appraises data from randomised controlled trials, to provide a synthesis of evidence to inform practice and research. We have not found any existing systematic review of this topic.

OBJECTIVES

To assess the efficacy and safety of re-feeding compared to discarding gastric residuals to improve growth in preterm infants. The allocation should have been started in the first week of life and should have been continued at least until the baby reaches full enteral feeds. The investigator could choose to discard the gastric residual in the re-feeding group, if the gastric residual quality is not satisfactory. However, the criteria for discarding gastric residual should have been pre-defined.

We will undertake subgroup analysis based on the gestational age ($\leq$ 27 weeks, 28 weeks to 31 weeks, $\geq$ 32 weeks), birth weight (< 1000 g, 1000 g to 1499 g, $\geq$ 1500 g), type of milk (human milk or formula milk), quality of the gastric residual (fresh milk, curded milk or bile-stained gastric residual), the volume of gastric residual replaced (total volume, 50% of the volume, volume of

the next feed or pre-specified volume irrespective of the volume of the aspirate, e.g. 2 mL, 3 mL, etc.), and whether the volume of gastric residual that is re-fed is included in or excluded from the volume of the next feed (Subgroup analysis and investigation of heterogeneity).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised trials and cluster-randomised trials will be included in the review.

Types of participants

Preterm infants (< 37 weeks' gestation).

Types of interventions

Intervention: Re-feeding the gastric residuals, unless the pre-defined quality parameters are not satisfied.
Note: The investigator could predefine the volume of gastric residual that would be re-fed, say, total volume, 50% of the volume, volume of the next feed or pre-specified volume irrespective of the volume of the aspirate (for example. 2 mL, 3 mL, etc), and whether the volume of residual that is re-fed would be included in or excluded from the volume of the next feed.
Comparison: Discarding the gastric residuals, irrespective of the quantity and quality.

Types of outcome measures

Primary outcomes

1. Time to regain birth weight (days) and subsequent rate of weight gain (g/kg/day), linear growth (cm/week) and increase in head circumference (cm/week) during the initial hospitalisation period
2. Number of infants with necrotising enterocolitis (NEC) stage 2 or 3 (Modified Bell's staging, Walsh 1986)

Secondary outcomes

1. Time to reach full enteral feeds of ≥ 150 mL/kg/day (days)
2. Episodes of interruption of feeds (lasting ≥ 12 hours)
3. Number of infants with extra-uterine growth restriction at discharge (number of infants who remain below the 10th percentile for the index population for weight, length and head circumference)
4. Number of days of total parenteral nutrition (TPN)
5. Number of infants with parenteral nutrition-associated liver disease
6. Number of days of central venous line (CVL) usage
7. Incidence of invasive infection as determined by culture of bacteria or fungus from blood, cerebrospinal fluid, urine, or from a normally sterile body space
8. All-cause mortality before discharge or up to 44 weeks' postmenstrual age
9. Duration of hospital stay (days)
10. Growth measures following discharge from hospital to latest follow-up
11. Neurodevelopmental outcomes assessed after 12 months corrected age: neurological evaluations; developmental scores; and classifications of disability, including auditory and visual disability. We will define neurodevelopmental impairment as the presence of one or more of the following: non-ambulant cerebral palsy; developmental quotient more than two standard deviations below the population mean; and blindness (visual acuity less than 6/60) or deafness (any hearing impairment requiring - or unimproved by - amplification).

Search methods for identification of studies

We will use the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register).We will search for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Electronic searches

We will conduct a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL, current issue) in the Cochrane Library; MEDLINE via PubMed (1996 to current); Embase (1980 to current); and CINAHL (1982 to current) using the following search terms: (gastric residual* OR aspirate*), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). We will not apply language restrictions. We will search clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International Trials Registry and Platform, and the ISRCTN Registry).

Searching other resources

We will examine reference lists in the included studies. We will search the proceedings of the annual meetings of the Pediatric Academic Societies (1993 to present), the European Society for Paedi-

atric Research (1995 to present), the Royal College of Paediatrics and Child Health (2000 to present), and the Perinatal Society of Australia and New Zealand (2000 to present). Trials reported only as abstracts will be eligible if sufficient information is available from the report, or from contact with the authors, to fulfil the inclusion criteria.

Additionally, we will review the reference lists of all identified articles for relevant articles not identified in the primary search.

Data collection and analysis

We will use the standard methods of Cochrane Neonatal (Higgins 2017).

Selection of studies

We will screen the title and abstract of all studies identified by the above search strategy and two review authors (TA and ST) will independently assess the full-text articles for all potentially relevant trials. We will exclude those studies that do not meet all of the inclusion criteria and we will state the reason for exclusion. We will discuss any disagreements until consensus is achieved.

We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009) and 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (TA and ST) will extract data independently using a data collection form to aid extraction of information on design, methodology, participants, interventions, outcomes and treatment effects from each included study. We will discuss any disagreements until we reach a consensus. If data from the trial reports are insufficient, we will contact the trialists for further information.

Assessment of risk of bias in included studies

Two review authors (TA and ST) will independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2017) for the following domains.

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Any other bias

Any disagreements will be resolved by discussion with the third author (UB). See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We will analyse the treatment effects in the individual trials using RevMan 2014 and report risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). We will determine the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis will be the participating infant in individually-randomised trials. For cluster-randomised trials, we will undertake analysis at the level of the individual while accounting for the clustering in the data using an estimate of the intra-cluster correlation coefficient (ICC) derived from the trial (if possible), or from another source (Higgins 2017). If ICCs from other sources are used, we plan to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we will synthesise the relevant information. We plan to combine the results where there is little heterogeneity between study designs and interactions between the effects of the intervention and the choice of randomisation unit is considered unlikely.

Dealing with missing data

We will request additional data from the trialists if data on important outcomes are missing or reported unclearly. Where data are still missing, we will examine the impact on effect size estimates in sensitivity analyses using the 'best-worst case scenario' technique.

Assessment of heterogeneity

We will examine the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We will calculate the I^2 statistic for each RR analysis to quantify inconsistency across studies and describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. Heterogeneity will be classified as none (< 25%); low (25% to 49%); moderate (50% to 74%); or high ($\geq$ 75%). If we detect moderate or high heterogeneity ($I^2 \geq 50\%$), we will explore the possible causes (for example, differences in study design, participants, interventions, or completeness of outcome assessments).

Assessment of reporting biases

If 10 or more trials are included in a meta-analysis, we will examine a funnel plot for asymmetry.

Data synthesis

We will analyse all infants randomised on an intention-to-treat basis and treatment effects in the individual trials using a fixed-effect model to combine the data. For meta-analyses of categorical outcomes we plan to calculate typical estimates of RR and RD, each with 95% CIs; for continuous outcomes we plan to calculate the mean difference (MD) if outcomes are measured in the same way between trials, and standardised mean difference (SMD) to combine trials measuring the same outcome using different scales. We will determine the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD. Where meta-analysis is judged to be inappropriate, we will analyse and interpret individual trials separately.

Quality of evidence

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: incidence of NEC and mortality.

Two review authors (TA and ST) will independently assess the quality of the evidence for each of the outcomes listed above. We will consider evidence from randomised controlled trials as high quality but downgrade the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We will use the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence. The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades.

1. High: We are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Subgroup analysis and investigation of heterogeneity

1. Based on gestational age - ≤ 27 weeks, 28 weeks to 31 weeks, ≥ 32 weeks
2. Based on birth weight - < 1000 g, 1000 g to 1499 g, ≥ 1500 g
3. Based on the type of milk - human milk or formula milk
4. Based on the quality of the gastric residual - fresh milk, curded milk or bile-stained residual
5. Based on the volume of gastric residual replaced - total volume, 50% of the volume, volume of the next feed or pre-specified volume irrespective of the volume of the aspirate (example: 2 mL, 3 mL, etc.)
6. Based on whether the volume of gastric residual that is re-fed, is included in or excluded from the volume of the next feed

Sensitivity analysis

We will undertake sensitivity analyses to determine if the findings are affected by including only studies of adequate methodology (low risk of bias), defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and less than 10% loss to follow-up.

ACKNOWLEDGEMENTS

The methods section of this protocol is based on a standard template used by Cochrane Neonatal.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Cochrane Neonatal standard search strategy

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))
Embase: ((exp infant) OR (infan* OR newborn or neonat* OR premature or very low birth weight or low birth weight or VLBW or LBW).mp AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp
CINAHL: (infan* OR newborn OR neonat* OR premature OR low birth weight OR VLBW OR LBW) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
CRS Web: (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. 'Risk of bias' tool

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the trials. For each trial, we will seek information regarding the method of randomisation, blinding and reporting of all outcomes of all the infants enrolled in the trial. We will assess each criterion as being at a low, high, or unclear risk of bias. Both review authors will separately assess each study. We will resolve any disagreement by discussion. We will add this information to the table 'Characteristics of included studies'. We will evaluate the following issues and enter the findings into the 'Risk of bias' table.

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we will categorise the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we will categorise the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we will categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as:

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we will categorise the methods used to blind outcome assessment. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorise the methods as:

- low risk (< 20% missing data);
- high risk ($\geq$ 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we will describe any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk;
- unclear risk

If needed, we plan to explore the impact of the level of bias through undertaking sensitivity analyses.

CONTRIBUTIONS OF AUTHORS

All the review authors contributed to the development of this protocol.

DECLARATIONS OF INTEREST

None known.

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