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Non-nutritive sucking for gastro-oesophageal reflux disease in preterm and low birth weight infants (Review)

Psaila K, Foster JP, Richards R, Jeffery HE

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[Intervention Review]

Non-nutritive sucking for gastro-oesophageal reflux disease in preterm and low birth weight infants

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ABSTRACT

Background

Gastro-oesophageal reflux (GOR) is commonly diagnosed in the neonatal population (DiPietro 1994), and generally causes few or no symptoms (Vandenplas 2009). Conversely, gastro-oesophageal reflux disease (GORD) refers to GOR that causes troublesome symptoms with or without complications such as damage to the oesophagus (Vandenplas 2009). Currently there is no evidence to support the range of measures recommended to help alleviate acid reflux experienced by infants. Non-nutritive sucking (NNS) has been used as an intervention to modulate neonatal state behaviours through its pacifying effects such as decrease infant fussiness and crying during feeds (Boiron 2007; Pickler 2004).

Objectives

To determine if NNS reduces GORD in preterm infants (less than 37 weeks' gestation) and low birth weight (less than 2500 g) infants, three months of age and less, with signs or symptoms suggestive of GORD, or infants with a diagnosis of GORD.

Search methods

We performed computerised searches of the electronic databases of the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 9, 2013), MEDLINE (1966 to September 2013), CINAHL (1982 to September 2013), and EMBASE (1988 to September 2013). We applied no language restrictions.

Selection criteria

Controlled trials using random or quasi-random allocation of preterm infants (less than 37 weeks' gestation) and low birth weight (less than 2500 g) infants three months of age and less with signs or symptoms suggestive of GORD, or infants with a diagnosis of GORD. We included studies reported only by abstracts, and cluster and cross-over randomised trials.

Data collection and analysis

Two review authors independently reviewed and selected trials from searches, assessed and rated study quality and extracted relevant data. We identified two studies from the initial search. After further review, we excluded both studies.

Main results

We identified no studies examining the effects of NNS for GORD in preterm and low birth weight infants

Authors' conclusions

There was insufficient evidence to determine the effectiveness of NNS for GORD. Adequately powered RCTs on the effect of NNS in preterm and low birth weight infants diagnosed with GORD are required.

PLAIN LANGUAGE SUMMARY

Non-nutritive sucking for gastro-oesophageal reflux disease in preterm and low birth weight infants

Background

Gastro-oesophageal reflux is the passage of the contents of the stomach into the oesophagus (feeding tube) with or without vomiting. It is relatively common in preterm infants and can sometimes lead to troublesome complications. Non-nutritive sucking is sucking on a dummy (pacifier) before, during, or after feeding by tube; before or after a bottle/breast feed; or outside of feeding times. It has been proposed as a way to reduce gastro-oesophageal disease in preterm infants.

Study characteristics

We searched scientific databases for clinical trials in preterm infants (born at less than 37 weeks' gestation) and low birth weight (less than 2500 g) at three months of age or less with signs or symptoms of gastro-oesophageal reflux.

Key results

We found no studies meeting our criteria. There is insufficient evidence from large clinical trials on the use of non-nutritive sucking for gastro-oesophageal disease in preterm and low birth weight infants.

Quality of the evidence

We found no studies meeting our criteria.

BACKGROUND

Description of the condition

Gastro-oesophageal reflux (GOR) is the passage of gastric contents into the oesophagus with or without regurgitation and vomiting (Carroll 2002; Vandenplas 2009). GOR is regarded as a normal physiological process that can occur several times per day and last less than three minutes during the postprandial period (after eating a meal) (Vandenplas 2009). GOR is commonly diagnosed in the neonatal population (DiPietro 1994), and generally causes few or no symptoms (Vandenplas 2009). Conversely, gastro-oesophageal reflux disease (GORD) refers to GOR that causes troublesome symptoms with or without complications such as damage to the oesophagus (Vandenplas 2009). Preterm or critically ill infants are at higher risk for the pathological form of reflux (DiPietro 1994).

The main factor that has been proposed as contributing to the development of GORD is the inappropriate relaxation of the lower oesophageal sphincter that results in acid reflux (Khalaf 2001; Davidson 2003), and damage to the oesophagus (Henry 2004; Huang 2002). GORD is an important cause of feeding and breathing problems in preterm infants (Jeffery 2000). It is associated with a range of adverse respiratory, gastrointestinal, and neurobehavioural effects. Adverse effects include pain (oesophageal or ear or both), wheezing, apnoea, stridor, recurrent bronchiolitis, episodes of oxygen desaturation, pneumonia, swallowing dysfunction, vomiting, coughing, choking and gagging, posseting (regurgitation of small quantities of milk after feeding), feed refusal, lower energy intake and excessive weight loss, fussiness during or following feeding, constant or sudden crying, irritability and sleep disturbances, delayed acquisition of oral sensorimotor feeding skills (disorganised and dysfunctional sucking or swallowing), delayed readiness for solid foods or food refusal, and delayed development (Hawdon 2000; Woodley 2009).

It has also been hypothesised that GOR can potentially trigger activation of the laryngeal chemoreflex during sleep and may, therefore, be implicated in sudden infant death syndrome (SIDS) (Molloy 2006; Page 2000). Several authors have reported a link between sleep states, movement, and the incidence and duration of GOR episodes (Jeffery 1983; Kahn 1991). Infants reportedly experience increased incidence and longer duration of GOR during states of wakefulness and active sleep as opposed to quiet sleep (Jeffery 1991). Reflexes that protect the airway against aspiration and provide respiratory defence against asphyxia are also depressed in active sleep compared with quiet sleep (Abu-Shaweesh 2004). While a direct causal link between GOR and SIDS cannot be claimed, GOR during active sleep combined with the presence of another mediating factor capable of depressing arousal (prone sleeping, prematurity, sedatives, seizures, or upper respiratory tract infections) could potentially lead to death. Preterm infants with GORD require longer hospital stays (Frakaloss 1998). Parental inability to feed and settle their infants to sleep can also negatively affect the parent-infant relationship (Vandenplas 2002).

The most sensitive objective measure of GORD is the pH probe, which tests for abnormal amounts of reflux of acidic stomach contents into the oesophagus; however, it does detect reflux that is alkalotic (pH greater than 7). The readings are based on the percentage of reflux time with pH less than 4 (reflux index) and the frequency and duration of the episodes (Wenzi 199). Another relatively new method for detecting GORD is the use of multiple intraluminal impedance that allows detection of reflux via changes in impedance caused by a liquid bolus inside the oesophagus, and is independent of pH (Peter 2002). Other methods of diagnosing GORD include upper gastrointestinal endoscopy and oesophageal biopsy to look for signs of GORD directly, such as inflammation or erosion (DeVault 2005).

Treatment and management of GORD is aimed at preventing or alleviating symptoms (Carroll 2002; Henry 2004). A range of measures has been recommended to help alleviate acid reflux experienced by infants. One non-Cochrane systematic review evaluated non-pharmacological and non-surgical therapies for GORD in infants (Carroll 2002). There was no evidence to support positioning, or thickening feed or juice with rice flour or carob bean gum preparation as interventions to prevent or reduce GORD. Changes to formula composition (e.g. casein-predominant, soy-based, or whey-predominant formulas) are ineffective in treating GORD (Carroll 2002).

Description of the intervention

Sucking is either nutritive or non-nutritive. Non-nutritive sucking (NNS) is defined as sucking on a dummy (pacifier) before, during, or after feeding by a nasogastric or orogastric tube; before or after a bottle/breast feed; or outside of feeding times (Pinelli 2005). NNS has been used as an intervention to facilitate transition from enteral to oral feeding, and to relieve neonatal pain and modulate neonatal state behaviours through its pacifying effects of reducing infant fussiness and crying during feeds (Boiron 2007; Pickler 2004).

How the intervention might work

Both physiological and behavioural mechanisms have been postulated for the beneficial effect of NNS on gastrointestinal functioning (Premji 2000). NNS accelerated the maturation of the sucking reflex, stimulated hormones/enzymes through the vagal innervation in the oral mucosa (thereby improving the digestion of enteral feeds), and helped increase weight gain in premature neonates (Pinelli 2005). While the role of NNS in the secretion of gastrin, motilin, and insulin is unclear, NNS may trigger the activity of sensory nerves in the oral mucosa to release these vagal-regulated gut hormones. This results in increased gastric acid secretion (Kanarek 1992), glucose-induced insulin (Widström 1988), and absorption of enteral feeding (Kanarek 1992; Premji 2000; Widström 1988). Lower levels of somatostatin have also been found in NNS infants resulting in increased gastric emptying (Widström 1988).

The effect of NNS on the maturation of the sucking reflex, gastric emptying, intestinal transit time, nutrient absorption, and weight gain have received increased attention in preterm infants (Orenstein 1988). One Cochrane review found that NNS reduced the time taken to return the neonate to a stable sleep state post-feeding (Pinelli 2005). Jeffery 1991 also found pH readings to be stable between 5 and 7 in preterm infants during quiet sleep.

NNS has been found to be protective for SIDS (Hauck 2005; Mitchell 2006). Several explanations have been proffered, such as pacifier use might alter tongue position (Cozzi 1979; Franco 2000), the infants' arousal level to apnoea, hypoxia is lowered when using a pacifier (Franco 2000; Kahn 2002). Several authors

have postulated that the decrease in SIDS among NNS infants was due to its effect in decreasing the rate of GORD (Mitchell 1993; Mitchell 2006; Morren 2002). Page 2000 and noted different responses to acid GOR between term and preterm infants. Similar to the response to acid GOR found in adults, term infants responded with increased swallowing, which in turn led to increased primary peristalsis. However, preterm infants did not increase pharyngeal swallowing, but rather increased propagated peristalsis. No satisfactory explanation of the protective mechanism of NNS has been found to date.

It has also been proposed that NNS reduces infant crying, which may reduce abdominal contractions, which in turn, may reduce episodes of gastric reflux (Button 2004). In addition, movement has been linked to increased occurrence and duration of GOR (Jeffery 1991; Kahn 1991). Therefore, it seems reasonable that NNS on a pacifier be encouraged.

North 2000 found that wheezing, earache, regurgitation of small quantities of milk after feeding (posseting) (Peters 2007), diarrhoea, and colic in infants up to six months of age increased with pacifier use. The non-Cochrane systematic review by Carroll 2002 concluded that there was no evidence to support NNS.

Why it is important to do this review

The question of whether NNS has an effect, positive or negative, on GORD in neonates remains unanswered. We have been unable to identify any previous Cochrane or non-Cochrane systematic reviews on the use of NNS for GORD.

OBJECTIVES

To determine if NNS reduces GORD in preterm infants (less than 37 weeks' gestation) and low birth weight (less than 2500 g) infants, three months of age and less, with signs or symptoms suggestive of GORD, or infants with a diagnosis of GORD.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all published and unpublished randomised controlled trials (RCTs) or quasi-RCTs eligible for inclusion in this review. Studies reported only in abstract form were eligible for inclusion. Cluster and cross-over randomised trials were eligible for inclusion in this review.

Types of participants

We included preterm infants (less than 37 weeks' gestation) and low birth weight (less than 2500 g) infants, three months of age and less, with signs or symptoms suggestive of GOR, or infants with a diagnosis of GOR based on 24-hour pH monitoring or oesophagitis on biopsy, or both.

We excluded infants who had undergone abdominal surgery and infants born with congenital anomalies of the gastrointestinal tract or anomalies that interfere with infant feeding. We also excluded infants on other potential therapies for GORD.

Types of interventions

NNS versus placebo or no treatment.

Types of outcome measures

Primary outcomes

GOR as diagnosed by pH metry, multiple intraluminal impedance, or endoscopy within two hours postprandial (after eating a meal).

Secondary outcomes

- GOR: number of episodes over a 24-hour period using pH metry or multiple intraluminal impedance.
- GOR: duration (i.e. number of minutes until clearance of any GOR episode over a 24-hour period using pH metry or multiple intraluminal impedance).
- GOR: duration of longest GOR episode in minutes (within two hours postprandial; over a 24-hour period) using pH metry or multiple intraluminal impedance.
- Days to full enteral feeding via an intragastric tube.
- Discontinuation of intervention.
- Weight gain (g/day).
- Apnoea (number over a 24-hour period): defined as any cessation of breathing for more than 20 seconds or a shorter pause associated with bradycardia or cyanosis within two hours postprandial.
- Apnoea requiring respiratory support.
- Oxygen desaturation (number over a 24-hour period): defined as any spontaneous fall in oxygen saturation (SpO_2) of 85% or less within two hours postprandial.
- Vomiting (total number over a 24-hour period).
- Behavioural disturbances (e.g. irritability, disruption in sleep pattern) documented on hospital record within two hours postprandial.
- Pain (as measured on validated measurement tool, e.g. The Neonatal Infant Pain Scale (NIPS), Preterm Infant Pain Profile (PIPP), Children's Hospital of Eastern Ontario Pain Scale (CRIES)): completed within two hours postprandial.
- Duration of hospital stay (total number of days from birth to discharge).
- Number of hospital re-admissions within the first year of life.
- Need for surgery (relating to GORD) (yes/no).
- Parent stress, satisfaction, or both (as measured on validated measurement tool, e.g. Parental Stressor Scale: Neonatal Intensive Care Unit).
- Death (prior to hospital discharge; within the first year of life).
- Aspiration pneumonia/pneumonitis (clinical or radiological (or both) evidence of lower respiratory tract compromise attributed to covert or evident aspiration of gastric contents).

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, and in press).

Electronic searches

We used the standard search strategy of the Cochrane Neonatal Review Group (neonatal.cochrane.org/), to search for RCTs in the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 9, 2013), MEDLINE (1966 to September 2013), EMBASE (1988 to September 2013), and CINAHL (1982 to September 2013), using the following subject headings (MeSH) and text words: [infant-

newborn OR infan*, OR Neonat*, OR Preterm* OR low birth weight] AND [non-nutritive sucking OR nonnutritive sucking] AND [gastro-oesophageal OR gastroesophageal OR infantile reflux OR reflux OR regurgitation OR gastric reflux, OR pH monitoring OR enteral feeding OR gastric feeding OR gastric emptying OR gastric regurgitation].

Searching other resources

We communicated with expert informants and searched bibliographies of reviews and trials for references to other trials. We also searched previous reviews including cross-references, abstracts, and conferences and symposia proceedings of the Perinatal Society of Australia and New Zealand, and Pediatric Academic Societies (American Pediatric Society/Society for Pediatric Research, and European Society for Paediatric Research) from 1990 to 2012. If we had identified any unpublished trials, we had planned to contact the corresponding investigator for information. We had intended to consider unpublished studies or studies only reported as abstracts as eligible for review if the study author could confirm the methods and data. We identified no unpublished studies. We contacted the study author of one RCT that was possible for inclusion for additional information about the study. We searched ClinicalTrials.gov (www.clinicaltrials.gov), Current Controlled Trials (www.controlled-trials.com), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) for ongoing or recently completed trials

Data collection and analysis

We used the standard systematic review methods of The Cochrane Collaboration as documented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two review authors (KP and JF) independently assessed all the potential studies identified as a result of the search strategy for inclusion. We resolved any disagreement through discussion.

Data extraction and management

Two review authors (KP and JF) worked independently to extract data and assess methodological quality and potential biases. We resolved disagreements by consensus. We completed a search log, showing databases searched and the dates of searches.

Assessment of risk of bias in included studies

We had planned to assess risk of bias for included studies using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We had planned to complete a 'Risk of bias' table addressing the following methodological issues.

Random sequence generation (checking for possible selection bias)

For each included study, we had planned to describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We would have assessed the risk of bias methods 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.

Allocation concealment (checking for possible selection bias)

For each included study, we had planned to describe the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We would have assessed the risk of bias methods 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.

Blinding (checking for possible performance bias)

For each included study, we had planned to describe the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We would have judged the study to be at low risk of bias if it was blinded or if we judged that the lack of blinding could not have affected the results. We would have assessed blinding separately for different outcomes and classes of outcomes. We would have assessed the risk of bias methods as:

- adequate, inadequate, or unclear for participants;
- adequate, inadequate, or unclear for personnel; or
- adequate, inadequate, or unclear for outcome assessors.

Incomplete outcome data (checking for possible attrition bias through withdrawals, drop-outs, and protocol deviations)

For each included study, we had planned to describe for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We would have stated 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 was reported, or could be supplied by the trial authors, we had planned to re-include missing data in the analyses. We would have assessed the risk of bias methods as:

- adequate (less than 20% missing data);
- inadequate; or
- unclear.

Selective reporting bias

For each included study, we had planned to describe how we investigated the possibility of selective outcome reporting bias and what we found. We would have assessed the risk of bias methods as:

- low risk (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review had been reported);
- high risk (where not all of the study's pre-specified outcomes had been reported; one or more reported primary outcomes

were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study did not include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

Other sources of bias

For each included study, we had planned to describe any important concerns that we had about other possible sources of bias (e.g. early termination of trial due to data-dependant process, extreme baseline imbalance, etc.). We would have assessed whether each study was free of other problems that could put it at risk of bias. We would have assessed other sources of bias as:

- low risk;
- high risk; or
- unclear.

Overall risk of bias

We planned to make judgements as to whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to the above, we would have assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings.

Measures of treatment effect

We had planned to analyse treatment effects using Review Manager 5 software (RevMan 2011).

We had intended to calculate the risk ratio (RR) and risk difference (RD) for dichotomous data. We planned to use the mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). We had planned to determine the number needed to treat for an additional beneficial outcome (NNTB) or harmful outcome (NNTH) for a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials and the neonatal unit (or subunit) for cluster randomised trials. See below for cross-over trials.

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually randomised trials. We planned to analyse them using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), or from another source (Higgins 2011). If ICCs from other sources had been used, we intended to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we had identified both cluster-randomised trials and individually randomised trials, we intended to synthesise the relevant information. We considered it reasonable to combine the results from both if there was little heterogeneity between the study designs, and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.

Cross-over trials

We intended to analyse the meta-analysis for cross-over trials as recommended by Elbourne 2002. In the absence of first-level evidence (parallel trials), we intended to include second-level evidence (cross-over design trials) in the analysis, in which we would use only data from the first treatment period. As such, we would have managed data as if it were extracted from a parallel trial. In the absence of second-level evidence, (if unable to extract the data from the first period only), we would have included third-level evidence using data from both treatment periods from cross-over design trials in the analysis. Hence, the analysis would have ignored the cross-over design of the trials.

Dealing with missing data

For all included studies, we intended to note levels of attrition. If data from the trial reports were insufficient, unclear, or missing, we intended to attempt to contact the trial authors for additional information.

We had intended to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analyses. For all outcomes, we intended to carry out analyses, as far as possible, on an intention-to-treat (ITT) basis, that is, we would attempt to include all participants randomised to each group in the analyses, and we would analyse all participants in the group to which they were allocated, regardless of whether they received the allocated intervention. The denominator for each outcome in each trial would be the number of randomised participants minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We had intended to use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we had identified substantial heterogeneity, we would have explored it by pre-specified subgroup analysis. We intended to grade the degree of heterogeneity as: less than 25%, unimportant; 25% to 49%, low; 50% to 74%, moderate; and greater than 75%, high heterogeneity.

Assessment of reporting biases

For each included study, we had intended to obtain the study protocol and we would have compared outcomes reported in the protocol with those reported in the findings for the included study. We planned to investigate reporting and publication bias by examining the degree of asymmetry of a funnel plot. Where we suspected reporting bias (see 'selective reporting bias' in Assessment of risk of bias in included studies section above), we had intended to contact study authors requesting missing outcome data.

Data synthesis

We had intended to use the fixed-effect model in Review Manager 5 for meta-analyses (RevMan 2011).

Subgroup analysis and investigation of heterogeneity

If possible, we had intended to explore potential sources of clinical heterogeneity through the following a priori subgroup analysis.

1. Gestational age (less than 28 weeks; 28 to 32 weeks; 32 to 37 weeks).

2. Low birth weight (less than 1000 g; 1000 to 1500 g; 1500 to 2500 g).
3. Strategies for exploring heterogeneity.
4. Identification of the methodological differences between studies.
5. Meta-regression, if sufficient data were available (Higgins 2011).

Sensitivity analysis

We had planned to explore methodological heterogeneity using sensitivity analyses. We would have assess studies at low risk of bias as those with adequate sequence generation, allocation concealment, and less than 10% losses with ITT analysis.

RESULTS

Description of studies

Results of the search

We found no studies meeting the eligibility criteria.

Included studies

We found no studies meeting the eligibility criteria.

Excluded studies

We excluded two studies (Orenstein 1988; Zhao 2004). One study did not include preterm or low birth weight infants (Orenstein 1988), and, in one study, infants did not demonstrate signs of GOR prior to study commencement (Zhao 2004).

Risk of bias in included studies

We found no studies meeting the eligibility criteria.

Effects of interventions

We found no studies meeting the eligibility criteria.

DISCUSSION

We identified two small RCTs that were initially thought to fit the criteria for inclusion in this review but were later excluded (Orenstein 1988; Zhao 2004).

We excluded one study from the review as the infant population did not include preterm or low birth weight infants (Orenstein 1988). This small cross-over trial evaluated the effect of pacifier use (NNS) on GOR in term infants less than six months of age. The study sought to determine whether positioning (prone versus sitting) had any effect on infants using versus not using a pacifier. The study found that pacifier use significantly affected only the frequency of reflux episodes, increasing it in prone infants from (mean ± standard deviation) 7.2 ± 1.1 to 12.8 ± 2.3 episodes/120 minutes postprandially (P value = 0.04) and decreasing it in seated infants from 21.1 ± 3.1 to 14.8 ± 2.6 postprandially (P value = 0.003) and from 17.3 ± 4.8 to 5.9 ± 0.9 in the fasting period (P value = 0.035). NNS did not significantly affect the clearance of reflux episodes or the total reflux time. These results suggest that infants with pathological reflux frequency might best avoid pacifier use while in the prone position. When a seated position is necessary, the pacifying effects of NNS may be useful in decreasing the number of reflux events as well as in reducing crying behaviour. The study did not evaluate the effects of NNS in the supine position.

We excluded one study due to signs of GOR not being demonstrated by infants prior to study commencement as determined in our inclusion criteria (Zhao 2004). The aim of the study was to evaluate the effects of NNS on gastric emptying and GOR in 38 premature infants born at less than 37 weeks' gestational age and feeding via intermittent nasogastric feeds. The number of episodes of GOR within a 24-hour period was significantly fewer in NNS than the control (no NNS) group (mean: 9, 95% CI 2 to 31 with NNS versus 14, 95% CI 5 to 31 with control; P value < 0.05). There was no significant difference in the number of GOR episodes lasting greater than five minutes or in the duration of longest GOR episode. Days to full enteral feeds in the NNS group were significantly shorter than in the control group (mean ± standard deviation: 12.36 ± 4.29 days with NNS versus 15.50 ± 4.58 days with control; P value < 0.05). Half gastric emptying time in the NNS group was significantly shorter than in the control group (mean ± standard deviation: 58.33 ± 22.94 minutes with NNS versus 73.75 ± 17.76 minutes with control; P value < 0.05). In addition, gastric residuals were significantly lower in the NNS than the control group (16.7% with NNS versus 50% with control; P value < 0.05). The incidence of vomiting or abdominal distension was lower in the NNS than the control group but this was not statistically significant (P value > 0.05). The total time of pH less than 4 and reflux index was lower in the NNS group but this was not statistically significant. In addition, the study identified no short-term adverse outcomes. Despite being excluded, the major findings from the small Zhao 2004 study show some promising results worth further investigation.

Summary of main results

We found no studies that were eligible for inclusion in this review.

Potential biases in the review process

We performed an extensive search of published and unpublished literature including searches of trial registries for ongoing studies. Two review authors independently assessed eligibility, study quality, and extracted data. We reached agreement through consensus.

Agreements and disagreements with other studies or reviews

We identified no eligible studies or reviews.

AUTHORS' CONCLUSIONS

Implications for practice

We identified no adverse outcomes for non-nutritive sucking (NNS). However, in view of the lack of evidence no recommendations for practice can be made.

Implications for research

Adequately powered randomised controlled trials on the effect of NNS in preterm and low birth weight infants diagnosed with gastro-oesophageal reflux disease are required. The results from the two small excluded studies provide some evidence that NNS may have some benefit in reducing the number of gastro-oesophageal reflux episodes. Future research should further evaluate the effect of NNS on both the length and frequency of gastro-oesophageal reflux episodes as determined in the outcome measures for this review. Studies should also evaluate whether positioning influences the effectiveness of NNS on reflux in preterm and low birth weight

infants. When this review is next updated, we will included positioning (prone, supine, upright, side-lying) as a subgroup.

ACKNOWLEDGEMENTS

None.

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Orenstein 1988	Infants not in gestational age range
Zhao 2004	Infants did demonstrate signs of gastro-oesophageal reflux prior to study commencement

CONTRIBUTIONS OF AUTHORS

All authors (KP, JF, RR, HJ) contributed to the writing of the protocol and review.

DECLARATIONS OF INTEREST

None.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Primary outcome in protocol "Diagnosis of gastro-oesophageal reflux disease by pH metry, multiple intraluminal impedance, or endoscopy within the first three months of life" changed in review to "Gastro-oesophageal reflux as diagnosed by pH metry, multiple intraluminal impedance, or endoscopy within two hours postprandial (after eating a meal)". Authors altered primary outcome to reflect clinical practice.

INDEX TERMS

Medical Subject Headings (MeSH)

*Pacifiers; Crying; Gastroesophageal Reflux [*therapy]; Infant, Low Birth Weight; Infant, Premature; Infant, Premature, Diseases [*therapy]

MeSH check words

Humans; Infant, Newborn