Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants (Review)

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[Intervention Review]

Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants

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ABSTRACT

Background

Scheduled interval feeding of prescribed enteral volumes is current standard practice for preterm infants. However, feeding preterm infants in response to their hunger and satiation cues (*ad libitum* or demand/semi demand) rather than at scheduled intervals might help in the establishment of independent oral feeding, increase nutrient intake and growth rates, and allow earlier hospital discharge.

Objectives

To assess the effect of a policy of feeding preterm infants on an *ad libitum* or demand/semi-demand basis versus feeding prescribed volumes at scheduled intervals on growth rates and the time to hospital discharge.

Search strategy

We used the standard search strategy of the Cochrane Neonatal Review Group. This included searches of the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 4, 2009), MEDLINE (1966 to Oct 2009), EMBASE (1980 to Oct 2009), CINAHL (1982 to Oct 2009), conference proceedings, and previous reviews.

Selection criteria

Randomised or quasi-randomised controlled trials (including cluster randomised trials) that compared a policy of feeding preterm infants on an *ad libitum* or demand/semi-demand basis versus feeding at scheduled intervals.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group with separate evaluation of trial quality and data extraction by two review authors.

Main results

We found eight randomised controlled trials that compared *ad libitum* or demand/semi-demand regimens with scheduled interval regimes in preterm infants in the transition phase from intragastric tube to oral feeding. The trials were generally small and of variable methodological quality. The duration of the intervention and the duration of data collection and follow-up in most of the trials was

not likely to have allowed detection of measurable effects on growth. Three trials reported that feeding preterm infants using an *ad libitum* or demand/semi-demand feeding regimen allowed earlier discharge from hospital (by about two to four days) but other trials did not confirm this finding.

Authors' conclusions

Limited evidence exists that feeding preterm infants with *ad libitum* or demand/semi-demand regimens allows earlier attainment of full oral feeding and earlier hospital discharge. This finding should be interpreted cautiously because of methodological weaknesses in the included trials. A large randomised controlled trial is needed to confirm this finding and to determine if *ad libitum* of demand/semi-demand feeding of preterm infants affects other clinically important outcomes.

PLAIN LANGUAGE SUMMARY

Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants

We identified eight small trials that examined whether feeding preterm infants in response to their own hunger cues is better than feeding set volumes of milk at predefined intervals. In general these were methodologically flawed and did not report on all important clinical outcomes. Some evidence was found to suggest that feeding preterm infants in response to their own hunger cues results in earlier hospital discharge by about 2 to 4 days. Further randomised controlled trials are needed to confirm this finding.

BACKGROUND

Description of the condition

The frequency of feeding and volume of milk intake of healthy term infants is generally dictated by the infant's appetite. Term infants can adjust their volume of intake to compensate for differences in the nutrient density of various milks (Fomon 1969; Fomon 1975). In contrast, enteral feeds for preterm infants are usually given at scheduled intervals using prescribed volumes (Siddell 1994). The rationale for using a scheduled interval feeding regime (without consideration of sleep or hunger status) is based on concerns about metabolic, gastrointestinal, and neurodevelopmental immaturity. However, there is some evidence that preterm infants may also have the ability to self-regulate their intake (Horton 1952; Tyson 1983). While hunger cues may be more difficult to detect in preterm infants, they may be sufficiently evident for a caregiver to recognise and respond to (Ross 2002).

Description of the intervention

Various alternatives to a strict scheduled interval feeding regimen for preterm infants have been described (Crosson 2004). These feeding strategies aim to respond to infant hunger cues and are particularly relevant to infants who are in the transition phase from gastric tube feeding to oral feeding (either breast, or bottle, or cup-feeding). At this stage (from about 32 to 34 weeks' postmenstrual age), preterm infants are usually developing sustained alert activity and a coordinated suck-swallow-breathe pattern (Bu'lock 1990; Holditch-Davis 2003).

Crosson 2004 has categorised these alternative feeding regimes as:

1. "*Ad libitum* feeding": The enteral feed starts in response to the infant's hunger cues and ends when the infant demonstrates satiation. The infant, therefore, determines the duration and volume of intake. Caregivers may preset a maximum duration of inactivity or sleep (generally more than five hours) between feeds after which infants are roused to feed.
2. "Demand feeding": The feed starts in response to the infant's hunger cues but ends when a prescribed volume of intake is reached. This strategy is more suited to infants who are receiving gastric tube feeds or who are fed orally from a bottle or cup. It is much more difficult to determine when the target volume of intake has been reached in breast fed infants.
3. "Semi-demand feeding": The infant's hunger cues are assessed at scheduled intervals. If hunger cues are noted the infant is offered a feed. If the infant is sleeping the assessment is delayed (usually by about 30 - 60 minutes). If hunger cues are then noted the infant is offered a feed. If the infant remains asleep then the infant is given a gastric tube feed. The volume of intake is generally prescribed.

How the intervention might work

Ad libitum or demand/semi-demand feeding regimens may be considered a part of an integrated approach to providing "developmental care" for preterm infants. The Cochrane review of other related components of developmental care found some evidence that interventions such as minimising unnecessary exposure to external stimuli and clustering of care activities increases nutrient intake and rates of growth and decreases the length of hospital stay (Symington 2006). Allowing preterm infants to dictate the timing and duration of enteral feeding may result in longer rest periods between some feeds, promote infant-determined sleep/wake patterns that reduce unnecessary energy expenditure and increase the total nutrient intake and increase growth rates (McCain 2003). It is also possible that allowing the infant to determine the pattern of enteral feeding will help in the development of organised behaviour states and the earlier establishment of full oral feeding, a key criterion for hospital discharge for preterm infants (AAP 2008). There may be other benefits for the family and caregivers, principally allowing parents to feel more directly involved with their infant's care and increasing their confidence and ability to recognise and respond to their infant's needs during their hospital stay and beyond.

Why it is important to do this review

Potential adverse effects of an *ad libitum* or demand/semi-demand regime for feeding preterm infants are also recognised. These usually relate to whether such a regimen can guarantee metabolic stability, particularly normoglycaemia, in this clinically vulnerable group. Even at the point of discharge from hospital, some preterm infants are known to be susceptible to hypoglycaemia if a scheduled enteral feed is omitted or delayed (Hume 1999). There is concern that repeated or prolonged episodes of hypoglycaemia may impair longer term growth and development (Duvanel 1999). There may be more acute problems relating to gastro-intestinal immaturity such as feeding intolerance and a higher risk of aspiration of gastric contents into the lungs. There are also concerns that allowing unrestrained volumes of enteral intake may increase the risk of necrotising enterocolitis.

OBJECTIVES

To assess the effect of a policy of feeding preterm infants on an *ad libitum* or demand/semi-demand basis versus feeding prescribed volumes at scheduled intervals on growth rates and time to hospital discharge.

We undertook separate comparisons of trials that compared *ad libitum* feeding with scheduled interval feeding and of trials that compared demand/semi-demand feeding with scheduled interval feeding.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled trials using random or quasi-random patient allocation. Cluster randomised trials where the unit of randomisation was a group of infants (for example, all infants cared for in a participating neonatal unit) were also eligible for inclusion. Cross-over studies that assessed the use of two feeding strategies in the same infant were not eligible for inclusion as this design would not permit a meaningful assessment of the effect of the intervention on the primary outcomes for this review (growth rates and time to hospital discharge). Studies published as abstracts were eligible for inclusion only if assessment of study quality was possible and if other criteria for inclusion were fulfilled. We contacted the authors of studies published as abstracts for further information if required.

Types of participants

Preterm infants (less than 37 weeks' gestation) at least partially enterally fed. Participating infants may have been fed with formula milk and/or human breast milk via any enteral route; enteral feeding tube, bottle, breast, or cup.

Types of interventions

Experimental:

1. *Ad libitum* feeding: The enteral feed starts in response to the infant's hunger cues and ends when the infant demonstrates satiation.
2. Demand/semi-demand feeding: The feed starts in response to the infant's hunger cues but ends when a prescribed volume of intake is reached. In semi-demand feeding, the infant may be given a gavage fed if he or she remains asleep beyond the predefined interval for assessing hunger cues.

Control:

1. Scheduled interval feeding: Feeds are given at scheduled intervals without regard to the infant's sleep or hunger status. Orally fed infants who are asleep are awakened to feed or fed via an enteral feeding tube if unable to be awoken sufficiently.

The infants in the comparison groups in each trial must have received the same type(s) of milk. Trials where the type of milk is a co-intervention were not eligible for inclusion (unless as part of a factorial design in the randomised controlled trial). Infant hunger

cues included crying, quiet wakefulness, hand to mouth gestures, and finger/fist sucking. Other hunger cues used by individual trialists were acceptable provided these had been defined in the trial protocol. Trials that used the response to non-nutritive sucking on a pacifier as a tool for assessing hunger in the intervention group were eligible for inclusion. However, we planned to interpret the findings of these trials with caution since the Cochrane review of non-nutritive sucking found evidence that this intervention shortens the transition from tube to bottle feeds, improves bottle feeding performance and behaviour, and is associated with a statistically significant decrease in length of hospital stay for preterm infants (Pinelli 2001). We did not specify a minimum trial duration as a primary eligibility criterion. However, we planned only to include growth data in meta-analyses from trials that allocated the intervention for a sufficient period (at least one week) to allow measurable effects on growth.

Types of outcome measures

Primary outcomes

1. Growth: (a) Weight gain (grams per day, or grams per kilogram per day); linear growth (millimetres per week); head circumference (millimetres per week); skinfold thickness (millimetres per week) during the trial period. (b) Proportion of infants who remain below the tenth percentile for the index population's distribution of weight, height, or head circumference when assessed at hospital discharge, 40 weeks postmenstrual age, during infancy, and beyond.
2. Duration of hospital admission: Postmenstrual age and/or chronological age (days from birth or from trial enrolment) to discharge to home from hospital.

Secondary outcomes

1. Age (postmenstrual age and days from birth) at establishment of full oral feeding (independent of intragastric tube feeding.
2. Nutrient intake during trial period: mean volume of milk and intake of calories/protein per kilogram per day.
3. Duration of breast feeding (time from start of trial until infant stops receiving any human breast milk) and breast feeding prevalence (any and exclusive) on discharge and at three and six months post term.
4. Milk aspiration: consistent clinical history and chest x-ray findings.
5. Hypoglycaemia requiring treatment with unscheduled enteral supplement or intravenous fluids or glucagon.
6. Feed intolerance defined as a requirement to cease enteral feeds and commence parenteral nutrition.
7. Necrotising enterocolitis: at least two of the following features: Pneumatosis coli on abdominal radiograph; abdominal distension or abdominal radiograph with gaseous distension or frothy appearance of bowel lumen (or both); blood in stool; lethargy, hypotonia, apnoea, or combination of these (Bell 1978).
8. Measures of parental satisfaction using validated assessment tools.
9. Neurodevelopmental outcomes at greater than 12 months corrected age measured using validated assessment tools such as Bayley Scales of Infant Development, and classifications of disability including auditory and visual disability. The composite outcome "severe neurodevelopmental disability" will be defined as any one or combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70), auditory and visual impairment.

Search methods for identification of studies

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

Electronic searches

This included electronic searches of the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 4, 2009), MEDLINE (1966 to Oct 2009), EMBASE (1980 to Oct 2009), and CINAHL (1982 to Oct 2009). The search strategy used the following text words and MeSH terms: Infant, Newborn OR Infant, Premature OR Infant, Low Birth Weight, OR Premature Birth, OR preterm OR low birth weight OR LBW OR premature; AND Infant-Nutrition OR Milk, Human OR Feeding Behavior, OR Sucking Behavior, OR oral feeding OR demand feeding OR semi-demand feeding OR self-regulatory feeding OR *ad libitum* OR feeding cues OR satiation. We limited the search outputs with the relevant filters for clinical trials. We did not apply any language restriction.

Searching other resources

The references in studies identified as potentially relevant were examined. The abstracts from the Society for Pediatric Research (1993 to 2009), the European Society for Pediatric Research (1995 to 2009) and the Royal College of Paediatrics and Child Health Spring Meeting (2000 to 2009) were searched. Trials reported only as abstracts were eligible if sufficient information was available from the report, or from contact with the authors, to fulfil the inclusion criteria.

The meta-Register of clinical trials (http://www.controlled-trials.com/mrct/search.html) and the US National Institutes of Health registry of clinical trials (http://clinicaltrials.gov/) web sites were searched for completed or ongoing trials.

Data collection and analysis

The standard methods of the Cochrane Neonatal Review Group were used.

Selection of studies

The title and abstract of all studies identified by the above search strategy were screened and the full articles for all potentially relevant trials obtained. The full text of any potentially eligible reports was reassessed and those studies that did not meet all of the inclusion criteria were excluded. Any disagreements were discussed until consensus was achieved.

Data extraction and management

A data collection form was used to aid extraction of relevant information from each included study. Each review author extracted the data separately. Any disagreements were discussed until consensus was achieved. If data from the trial reports were insufficient, the investigators were contacted for further information.

Assessment of risk of bias in included studies

The criteria and standard methods of the Cochrane Neonatal Review Group were used to independently assess the methodological quality of any included trials in terms of allocation concealment, blinding of parents or caregivers and assessors to the intervention and completeness of assessment in all randomised individuals. Additional information from the trial authors was requested to clarify methodology and results as necessary. This information was added to the Characteristics of Included Studies Table.

In addition, for the update in 2009, the following issues were evaluated and entered into 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

Relative risk (RR) and risk difference (RD) were calculated for dichotomous data and weighted mean difference (WMD) for continuous data, with respective 95% confidence intervals (CI). The number needed to treat for benefit (NNTB) or harm (NNTH) was determined for a statistically significant difference in the RD.

Assessment of heterogeneity

For meta-analyses, we planned to estimate the treatment effects of individual trials and examine heterogeneity between trial results 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

We planned to use a fixed effects model for meta-analyses.

Subgroup analysis and investigation of heterogeneity

If sufficient data were available, we planned to undertake additional subgroup analyses of:

1. trials where all participating infants were enterally fed via gastric tubes (no oral feeding);
2. trial where participating infants were in transition from gastric tube to oral feeds;
3. trials where all participating infants were fed orally (no gastric tube feeding);
4. trials where all participating infants were exclusively fed from the breast;
5. trials where the infants' responses to non-nutritive sucking were used to assess hunger;
6. cluster randomised controlled trials.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Included studies

Eight trials fulfilled the review inclusion criteria and these are described in detail in the table, Characteristics of included studies (Collinge 1982; Kansas 2004; McCain 2001; Pridham 1999; Pridham 2001; Puckett 2008; Saunders 1991; Waber 1998). One study is published in abstract form only (Kansas 2004). The principal investigator provided further details to allow assessment of methodological quality and extraction of outcomes data.

Population: All of the included studies were undertaken since 1980 by investigators attached to neonatal units in North America. The trials in general were small. 496 infants in total participated. The participants in all of the trials were clinically stable preterm infants who were fully enterally fed and at transition from intragastric tube feeds to oral feeds (generally between 32 and 36 weeks' postmenstrual age). Most of the trials specifically excluded infants who were small for gestational age at birth and infants with congenital anomalies or gastrointestinal or neurological problems. The balance of oral versus tube feeding at enrolment differed between trials. One trial enrolled infants at the start of transition to oral feeding when infants were mainly fed via an intragastric tube (McCain 2001). In the other trials, infants were enrolled later in the transition phase when infants were receiving most of their feeds orally. In six trials, intragastric feeding tubes were removed when infants were allocated to the intervention group (Kansas 2004; Waber 1998; Collinge 1982; Pridham 1999; Pridham 2001; Puckett 2008).

Intervention: We classified five trials as comparing *ad libitum* feeding with scheduled interval feeding (Collinge 1982; Kansas 2004; Pridham 1999; Pridham 2001; Puckett 2008). *Ad libitum* feeding was generally described in the trial reports as allowing the infant to feed orally in response to hunger cues such as crying, sucking on fingers/pacifier, or rooting. Feeding was ceased only in response to satiation cues such as sleep of failure to maintain sucking. In Puckett 2008 infants were aroused to feed orally if had not demonstrated sufficient huger cues by five hours after the previous feed.

We classified three trials as comparisons of demand/semi-demand feeding with scheduled interval feeding (McCain 2001; Saunders 1991; Waber 1998). In two trials this meant that infants were fed in response to standard hunger cues (Saunders 1991; Waber 1998). If infants did not demonstrate these cues within five hours, infants were aroused to feed orally or given a prescribed volume of milk via an intragastric tube. In the other trial, the infant's readiness to feed was assessed every three hours by the response to non-nutritive sucking (McCain 2001). Oral feeds were stopped when the infant stopped sucking or fell asleep. If the minimum prescribed amount was not taken the infants received a prescribed volume via the intragastric tube.

Scheduled interval feeding was generally defined as regular feeding either orally or via an intragastric feeding tube at three to four hourly intervals to achieve an prescribed intake. The target volume of intake in the trials varied from 100 to 160 ml/kg/day. In all of the trials the infants in the intervention and control groups received the same type(s) of milk. Most trial protocols permitted infants to receive either breast milk or formula milk or a mixture of these. One trial recruited only formula milk fed infants (Saunders 1991).

Outcomes: Most trials assessed only short-term outcomes, principally volume and calorie intake and growth parameters (usually weight) during the study period. The duration of study period was less than seven days in six of the trials. In the other trials the intervention was continued until the infants were assessed as being ready for discharge home, typically 10 to 14 days (Kansas 2004; Puckett 2008).

Excluded studies

Four studies were excluded (Anderson 1990; Chang 2004; Horton 1952; Kirk 2007). The reasons for exclusion are listed in the table, Characteristics of excluded studies. Anderson 1990 assessed the effect of a range of nipples for bottle feeding and for non-nutritive sucking but did not specifically assess *ad libitum* or demand/semi-demand feeding versus scheduled interval feeding. Chang 2004 described a randomised crossover study in which 11 preterm infants were randomly allocated to receive *ad libitum* feeds for 48 hours followed by scheduled interval feeds for 48 hours or vice versa. Because this study design does not allow the collection of meaningful data on growth and time to hospital discharge, the primary outcomes of this review, the trial was not considered eligible for inclusion. Horton 1952 reported a case series of low birth weight infants who received demand oral feeds. Kirk 2007 reported an epoch-comparison of outcomes for infants demand-fed versus historical schedule interval fed controls.

Risk of bias in included studies

The methodological quality of the included trials varied. Five reports described a randomisation procedure that is likely to have achieved satisfactory allocation concealment. Because of the nature of the intervention, parents and caregivers were not blinded in any of the trials. It is unlikely that outcome assessment was blinded in any of the trials as the primary outcomes (nutrient intake and weight gain) were assessed by caregivers. Follow-up was complete or near-complete in six of the trials, but not for two trials (Pridham 1999; Pridham 2001) where 92 of the 199 (46%) enrolled infants were discharged home before completing the prespecified five days study period. Outcome data were not recorded for these infants.

Effects of interventions

AD LIBITUM FEEDING VERSUS SCHEDULED INTERVAL FEEDING (Comparison 1):

Four trials: Collinge 1982; Kansas 2004; Pridham 1999; Pridham 2001; Puckett 2008)

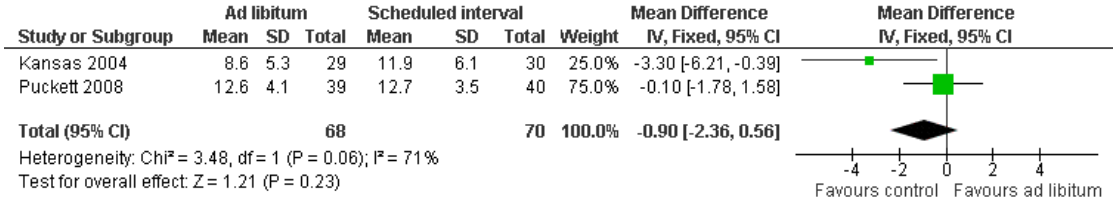
Primary Outcomes

Growth (four trials reported data) (Outcome 1.1):

(a) Kansas 2004 and Puckett 2008 reported that the rate of weight gain in the trial period. Meta-analysis did not detect a statistically significantly difference: WMD -0.9 [-2.4, 0.6] g/kg/day (I^2 = 71%) (Figure 1). Collinge 1982 reported that the mean daily weight gain in the three-day study period did not differ significantly between the groups (11.2 g versus 14.6 g; SD not reported

or available from investigators). Both Pridham 1999 and Pridham 2001 reported that there was not a statistically significant difference in the rate of weight gain (g/kg/day) during the five days study period. These data were presented in graphs and applied only to the infants who were not discharged home before completing the pre-specified five days study period. These data are not available (personal communication from the principal investigator).

Figure 1. Forest plot of comparison: 1 Ad libitum feeding versus scheduled interval feeding, outcome: 1.1 Growth: weight change during study period (grams per kilogram per day).



None of the trials collected data on linear growth, head circumference growth, or changes in skinfold thickness during the trial period.

(b) None of the trials collected any data on longer term growth parameters.

Postmenstrual age and/or postnatal age (days from birth or from trial enrolment) to discharge to home from hospital (five trials reported data) (Outcomes 1.2 - 1.3):

Kansas 2004 reported that there was not a statistically significant difference in postmenstrual age or postnatal age (days from birth) at discharge from hospital (Figure 2). Puckett 2008 reported that the postmenstrual age at discharge was statistically significantly lower in infants in the intervention group: MD -0.7 (95% CI -1.26 to -0.14) weeks. Meta-analysis of data from both trials found a statistically significantly lower postmenstrual age at discharge in the intervention group: MD -0.48 (95% CI -0.94 to -0.01) weeks. (Figure 3).

Figure 2. Forest plot of comparison: 1 Ad libitum feeding versus scheduled interval feeding, outcome: 1.2 Age at discharge (days).

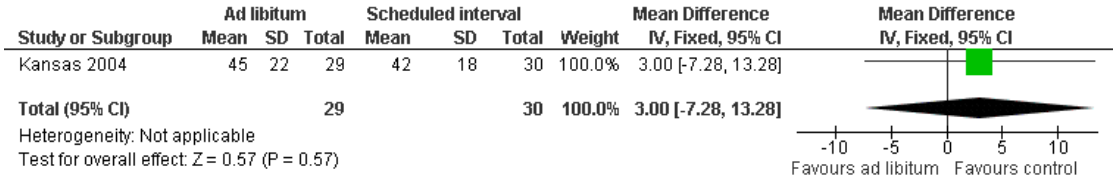
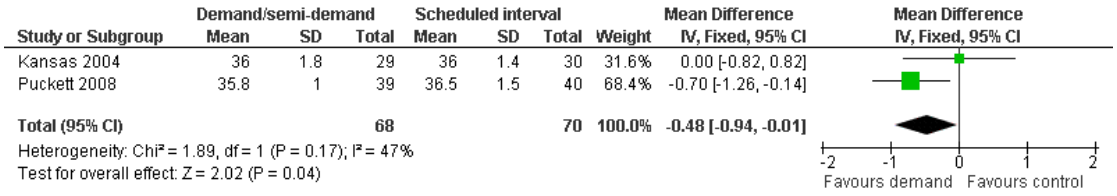


Figure 3. Forest plot of comparison: 1 Ad libitum feeding versus scheduled interval feeding, outcome: 1.3 Postmenstrual age at discharge (weeks).



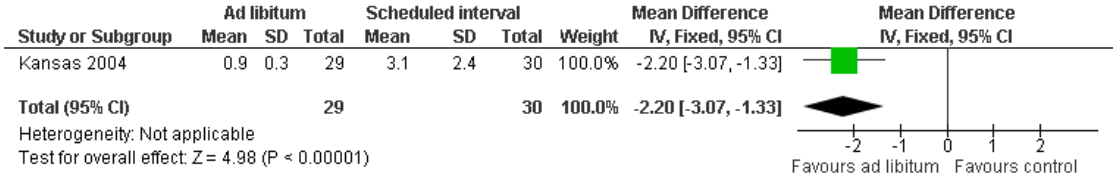
Collinge 1982 did not report age at discharge but did state that there was a statistically significantly difference in the number of days from study enrolment until infants were ready for hospital discharge: 2.7 days versus 8.9 days. SD were not reported or available from the trial investigators. Pridham 1999 and Pridham 2001 did not report age at hospital discharge but stated that there was not a statistically significant difference in the duration of hospital stay following randomisation.

Secondary Outcomes

Time to establishment of full oral feeds (two trials reported data) (Outcome 1.4):

Kansas 2004 reported a statistically significant difference in the time taken to achieve full oral feeding after trial entry: MD -2.2 (95% CI -3.1 to -1.3) days (Figure 4). Collinge 1982 reported that the intervention group achieved establishment of full oral feeds independent of tube feeding earlier than the control group but did not comment on statistical significance or provide data to assess statistical significance.

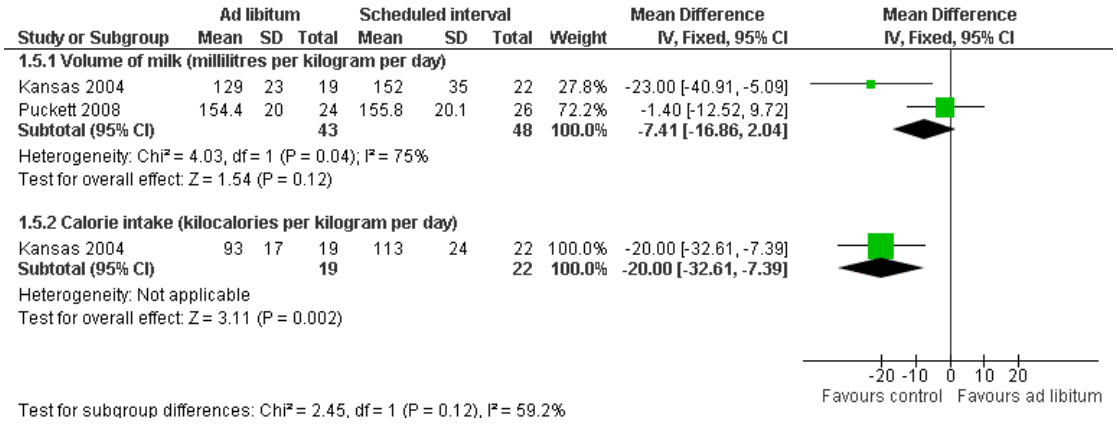
Figure 4. Forest plot of comparison: 1 Ad libitum feeding versus scheduled interval feeding, outcome: 1.3 Time to establishment of full oral feeds (after trial entry).



Nutrient intake during trial period (five trials reported data) (Outcome 1.5):

Kansas 2004 and Puckett 2008 reported that the daily volume of intake during the study period for those infants who were not breast fed (since it was not possible to measure nutrient intake of breast feeding infants). Meta-analysis did not detect a statistically significant difference: WMD -7.4 (-16.9 to 2.0) ml/kg/day (I^2 = 75%) (Figure 5). Kansas 2004 reported that the intervention group received statistically significantly fewer calories: MD -20.0 (95% CI -32.6 to -7.4) calories/kg/day (Figure 5).

Figure 5. Forest plot of comparison: 1 Ad libitum feeding versus scheduled interval feeding, outcome: 1.4 Nutrient intake during trial period (non breast fed infants only).



Collinge 1982 reported that during the three-days study period the infants allocated to demand feeding received significantly fewer feeds per day (5.1 in the study group versus 7.8 in the control group) and a significantly lower number of gavage feeds per day (0.1 in the study group versus 4.6 in the control group). The total average milk intake did not differ between the groups (154.9 ml/kg/day in the study group versus 154.4 ml/kg/day in the control group). SD were not reported or available from the trial investigators.

Pridham 1999 and Pridham 2001 both reported that calorie intake was lower in the *ad libitum* group than the control group during the five days study period. The reports do not state whether this difference was statistically significant. The mean daily calorie intake data were presented in graphs and applied only to the enrolled infants were not discharged home before completing the pre-specified five days study period. We could not extract the data for statistical analyses. However, the graphs illustrate that the standard errors for intervention and control groups for each daily mean calorie intake in each of the trials overlapped suggesting that differences were not statistically significant.

Duration of breast-feeding: Not reported in any of the included studies.

Milk aspiration: Not reported in any of the included studies.

Hypoglycaemia: Not reported in any of the included studies.

Feed intolerance: Not reported in any of the included studies.

Necrotising enterocolitis: Not reported in any of the included studies.

Measures of parental satisfaction: Not reported in any of the included studies.

Neurodevelopmental outcomes: Not reported in any of the included studies.

DEMAND/SEMI-DEMAND FEEDING VERSUS SCHEDULED INTERVAL FEEDING (Comparison 2):

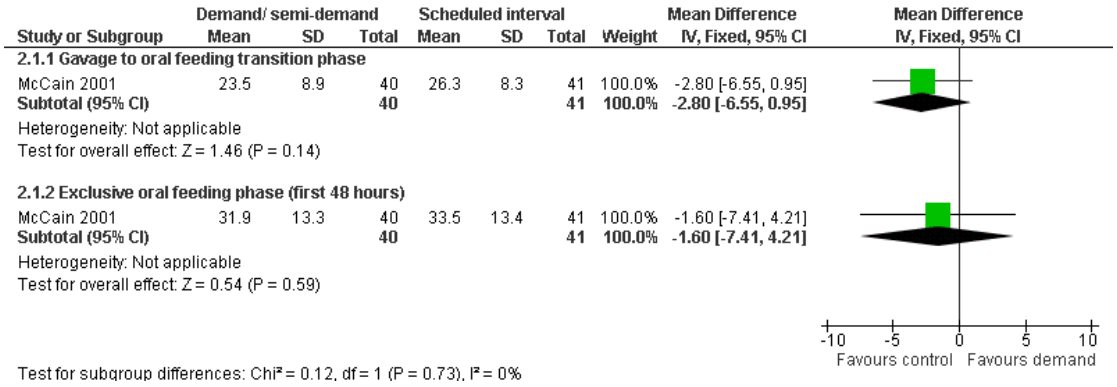
Three trials: McCain 2001; Saunders 1991; Waber 1998)

Primary Outcomes

Growth (three trials reported data) (Outcome 2.1):

(a) McCain 2001 reported that there was not a statistically significant difference in the rate of weight gain during two phases of the study period: (i) Gavage-to-oral feeding phase (average duration 5 days in the intervention group versus 10 days in the control group: see below): 23.5 (SD 8.9) g/day in the intervention group versus 26.3 (SD 8.3) g/day in the control group, (ii) First 48 hours of exclusive oral feeding phase: 31.9 (SD 13.3) g/day in the intervention group versus 33.5 (SD 13.4) g/day in the control group (Figure 6).

Figure 6. Forest plot of comparison: 2 Demand/semi-demand feeding versus scheduled interval feeding, outcome: 2.1 Growth: weight gain during study period (grams per day).



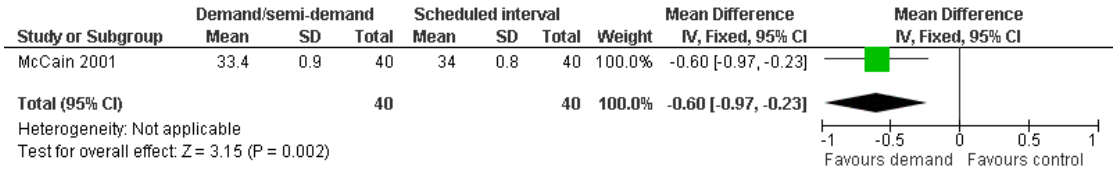
Saunders 1991 reported that there was not a statistically significant difference in the rate of weight gain (grams per day) during the six days study period. These data were presented in graphs only. Waber 1998 reported that the average daily weight gain in the intervention group was 26.4 grams versus 34.1 grams in the control group. The authors did not state whether this difference was statistically significant. Standard deviations were not reported. None of the trials provided data on linear growth, head circumference growth, or changes in skinfold thickness during the trial period.

(b) None of the trials reported any data on longer term growth parameters.

Postmenstrual age and/or postnatal age (days from birth or from trial enrolment) to discharge to home from hospital (four trials reported data) (Outcome 2.2):

McCain 2001 reported that the postmenstrual age at discharge was statistically significantly lower in infants in the intervention group (34.0 weeks; SD 0.8 weeks) compared to control infants (33.4 weeks; SD 0.9 weeks): MD -0.6 (95% CI -0.97 to -0.23) weeks (Figure 7).

Figure 7. Forest plot of comparison: 2 Demand/semi-demand feeding versus scheduled interval feeding, outcome: 2.4 Postmenstrual age at discharge (weeks).



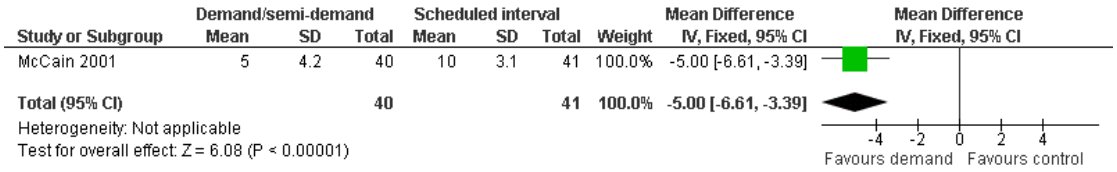
Saunders 1991 did not report age at hospital discharge but did state that there was not a statistically significant difference in the duration of hospital stay following randomisation: 7.2 days in the intervention group versus 8.4 days in the control group. SD were not reported. Further data are no longer available from the principal investigator. Waber 1998 reported that the duration of hospital stay was 31 days in the intervention group versus 33 days in the control group. The authors did not state whether this difference was statistically significant. SD were not reported. We sought but did not obtain further data from the trial authors.

Secondary Outcomes

Time to establishment of full oral feeds (one trial reported data) (Outcome 2.3):

McCain 2001 reported a statistically significant difference in the number of days from trial entry to establishment of full oral feeds: 5.0 (SD 4.2) days in the intervention group versus 10.0 (SD 3.1) days in the control group: MD -5.0 (95% CI -6.6 to -3.4) days (Figure 8).

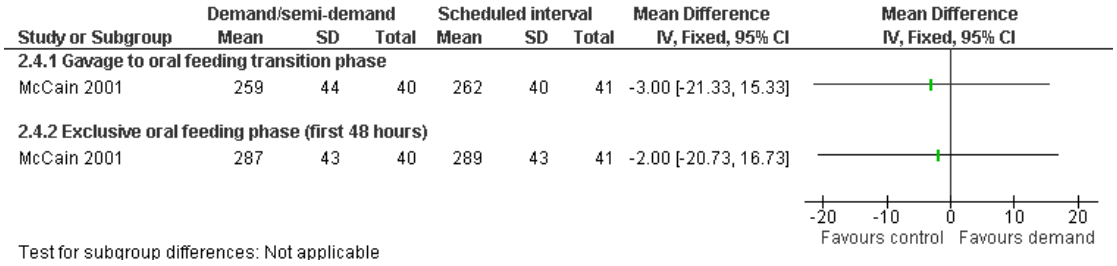
Figure 8. Forest plot of comparison: 2 Demand/semi-demand feeding versus scheduled interval feeding, outcome: 2.5 Time to establishment of full oral feeds (days after trial entry).



Nutrient intake during trial period (two trials reported data) (Outcomes 2.4 - 2.5):

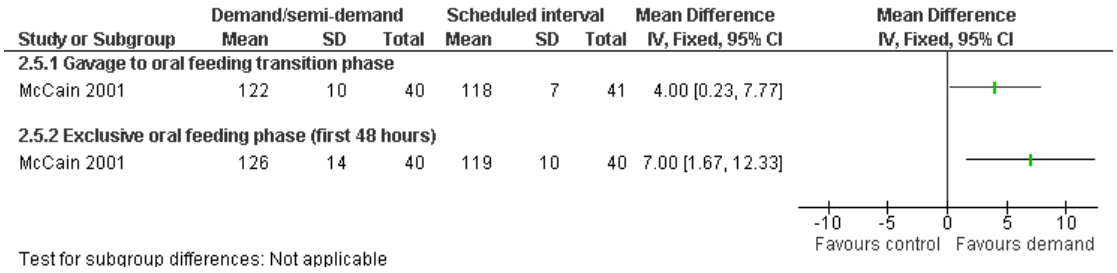
McCain 2001 reported that there was not a statistically significant difference in volume of milk intake during two phases of the study period: (i) Gavage-to-oral feeding phase (average duration 5 days in the intervention group versus 10 days in the control group): MD -3.0 (95% CI -21.3 to 15.3) ml/day, (ii) First 48 hours of exclusive oral feeding phase: MD -2.0 (95% CI -20.7 to 16.7) ml/day (Figure 9).

Figure 9. Forest plot of comparison: 2 Demand/semi-demand feeding versus scheduled interval feeding, outcome: 2.4 Nutrient intake during the trial period (millilitres per day).



McCain 2001 reported that the average daily intake of calories was statistically significantly higher in the intervention group during the two phases of the study period: (i) Gavage-to-oral feeding phase: MD 4.0 (95% CI 0.2 to 7.8) calories/kg/day, (ii) First 48 hours of exclusive oral feeding phase: MD 7.0 (95% CI 1.7 to 12.3) calories/kg/day (Figure 10).

Figure 10. Forest plot of comparison: 2 Demand/semi-demand feeding versus scheduled interval feeding, outcome: 2.5 Calorie intake during the trial period (per kilogram per day).



Waber 1998 reported that (i) the average calorie intake was 88.7 calories/kg/day in the intervention group versus 115.6 calories/kg/day in the control group, (ii) the average protein intake was 2.5 g/kg/day in the intervention group versus 3.4 g/kg/day in the control group, and (iii) the average fluid intake was 119.1 ml/kg/day in the intervention group versus 146.8 ml/kg/day in the control group. The authors did not state whether any of these differences were statistically significant. SD were not reported and are not available from the trial authors. Saunders 1991 did not collect data on nutrient intake (personal communication from principal investigator).

Duration of breast-feeding: Not reported in any of the included studies.

Milk aspiration: Not reported in any of the included studies.

Hypoglycaemia: Not reported in any of the included studies.

Feed intolerance: Not reported in any of the included studies.

Necrotising enterocolitis: Not reported in any of the included studies.

Measures of parental satisfaction: Not reported in any of the included studies.

Neurodevelopmental outcomes: Not reported in any of the included studies.

SUBGROUP ANALYSES:

1. Trials where all participating infants were enterally fed via gastric tubes (no oral feeding): None of the trials belonged to this subgroup.
2. Trial where participating infants were in transition from gastric tube to oral feeds: All of the trials belonged to this subgroup.
3. Trials where all participating infants were fed orally (no gastric tube feeding): None of the trials belonged to this subgroup.
4. Trials where all participating infants were exclusively fed from the breast: None of the trials belonged to this subgroup.
5. Trials where the infants' responses to non-nutritive sucking were used to assess hunger. One trial belonged to this subgroup (McCain 2001). See above for trial description and findings.
6. Cluster randomised controlled trials: We did not identify any cluster randomised controlled trial.

DISCUSSION

The available data from randomised controlled trials do not provide strong evidence that *ad libitum* or demand/semi-demand feeding affects clinically important outcomes for preterm infants. The methodological quality of the trials varied and, therefore, the findings should be interpreted cautiously. In most trials, limitations in the way the data were reported did not allow evaluation of the statistical significance of reported differences in outcomes or inclusion of the findings in meta-analyses.

The primary outcomes for this review were growth rates and age at hospital discharge. Most of the trials did not report statistically significant differences in growth rates for infants fed *ad libitum* or demand/semi-demand compared to infants fed at scheduled intervals. However, the duration of the intervention and the duration of data collection and follow up (less than five days) in these trials is not likely to have allowed detection of measurable effects on growth. Only two trials assessed growth for longer than one week (up to about 10 to 14 days). One study found that the rate of weight gain was lower in the *ad libitum* fed infants (Kansas 2004). The clinical significance of this finding is unclear as the trial did not find a statistically significant difference in the weight nor the age at discharge.

Three of the included trials reported that infants fed *ad libitum* or demand/semi-demand were discharged home several days earlier than infants in the scheduled interval feeding group (Collinge 1982; McCain 2001; Puckett 2008). The other trials did not confirm this finding. Additionally, since McCain 2001 used non-nutritive sucking on a pacifier to assess readiness to feed, the finding in that trial of a shortened time to hospital discharge should be interpreted cautiously since evidence exists that non-nutritive sucking shortens reduces the length of hospital stay for preterm infants (Pinelli 2001).

With regard to secondary outcomes, three of the included trials reported that *ad libitum* or demand/semi-demand feeding shortened the duration of the transition phase from tube to full oral feeds. The relevance of this finding is unclear as most trials enrolled infants when they were already mainly fed orally (at which point intragastric feeding tubes were removed from infants in the intervention group). Only one of the trials recruited infants at the start of transition to oral feeding phase (McCain 2001). However, as discussed above, the findings from this trial should be interpreted cautiously because of the possibility that non-nutritive sucking itself shortens the transition from tube to oral feeds for preterm infants (Pinelli 2001).

One trial reported that nutrient intake was lower during the study period for those infants fed *ad libitum*, consistent with the finding that infants fed *ad libitum* had lower rates of weight gain (Kansas 2004). Paradoxically, the infants fed *ad libitum* also had less variance in the quantity of nutrient intake. This may be due to variation in the prescribed volume of intake in the scheduled interval feeding group- from 110 to 150 millilitres per kilogram per day depending on postnatal age at enrolment. Conversely, the trial that assessed the effect of demand/semi-demand feeding using the infant's response to non-nutritive sucking to assess readiness to feed reported that infants in the intervention group had a greater intake of calories during the study period (McCain 2001). The clinical significance of this marginal difference (about four to seven calories per kilogram per day) is unclear. None of the other trials reported that *ad libitum* or demand/semi-demand feeding affected nutrient intake but in general the data reported are not sufficient to assess statistical significance and differences in study design limited the validity of data synthesis.

AUTHORS' CONCLUSIONS

Implications for practice

The currently available data are not sufficient to determine whether feeding *ad libitum* or demand/semi demand versus feeding prescribed volumes at scheduled intervals improves outcomes for preterm infants. Although some limited evidence exists that feeding preterm infants with *ad libitum* or demand/semi-demand regimens allows earlier attainment of full oral feeding and earlier hospital discharge, this finding should be interpreted and applied cautiously because of methodological weaknesses in the included trials.

Implications for research

There is a need for a large pragmatic randomised controlled trial to assess whether an *ad libitum* or demand/semi-demand feeding regimen (versus scheduled interval feeding) affects important clinical outcomes for preterm infants and their families. Such a trial should probably focus first on those infants at the transition from enteral tube to oral feeding. The involvement of parents groups in the design of the trial would inform the selection of the most relevant outcomes including those related to parental satisfaction.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Collinge 1982

Methods	Blinding of randomisation: can't tell Blinding of intervention: no Complete follow-up: yes Blinding of outcome measurement: can't tell
Participants	36 preterm infants, birth weight less than 2500 grams and appropriate for gestational age. Infants were recruited when they weighed at least 1800 grams and were fully enterally fed and receiving at least one feed per day by gavage via an intragastric feeding tube. Breast milk fed and formula milk fed infants (or mixed) participated in the trial. Formula fed infants received either standard calorie milk or calorie and protein enriched ("low birth weight") formula milk, or both. There is no indication in the report that the choice of type of formula milk was associated with the feeding regime allocation. Infants with severe gastrointestinal or neurological problems were not eligible to participate.
Interventions	Intervention (N=18): "*Ad libitum*" feeding, defined in the trial report as "allowing the infant to feed as frequently as (s)he wishes, and to take as much as desired at each feeding". Infants were fed (orally or via a gastric feeding tube) in response to crying, sucking on fingers/pacifier, activity and rooting. The trial report does not state which satiation cues were assessed. Control (N= 18) received prescribed volumes of milk (up to 160 ml/kg/day) either orally or via a feeding tube at three to four hourly intervals.
Outcomes	Volume of intake, and calorie-intake during trial period. Total number of feeds per day, and number of feeds given via gastric feeding tube per day. Time from randomisation to discharge from hospital.
Notes	Setting: Montreal Children's Hospital, Canada. 1981-1982. We have contacted the trial investigators to seek further information on methodology and results.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Blinding of randomisation: can't tell
Allocation concealment?	Unclear	Blinding of randomisation: can't tell
Blinding? All outcomes	No	Blinding of intervention: no Blinding of outcome measurement: can't tell

Collinge 1982 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Complete follow-up: yes
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Kansas 2004

Methods	Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: yes Blinding of outcome measurement: no
Participants	59 preterm infants (born before 33 weeks' gestational age) who were able to take at least half of their enteral feeds orally from a nipple (either bottle or breast).
Interventions	Intervention (N= 29): "*Ad libitum*" feeding: At randomisation, enteral feeding tubes were removed and infants were then fed *ad libitum* (no maximum or minimum feeding volume or interval) via a nipple in response to hunger and satiation cues. Control (N= 30) scheduled interval feeding with gavage feeding if infant did not ingest prescribed volume from nipple.
Outcomes	Days (from birth) to discharge to home from hospital. Daily weight gain, and weight at discharge. Days (from randomisation) to full nipple feeding. Average daily volume/calorie intake.
Notes	Setting: duPont Hospital for Children, Philadelphia, USA. 2003. Reported in abstract form only. Further information on methodology kindly provided by trial investigators.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Blinding of randomisation: yes
Allocation concealment?	Yes	Blinding of randomisation: yes
Blinding? All outcomes	No	Blinding of intervention: no Blinding of outcome measurement: no
Incomplete outcome data addressed? All outcomes	Yes	Complete follow-up: yes
Free of selective reporting?	Yes	

McCain 2001

Methods	Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: yes Blinding of outcome measurement: no
Participants	81 preterm infants of postmenstrual age between 32 to 34 weeks who were fully enterally-fed. Infants with severe periventricular haemorrhage, congenital anomalies, or gastrointestinal or neurological problems were not eligible to participate. Infants were fed fortified human milk or commercial formula at 105 to 130 kcal/kg/day per nursery standard of care. The infants had indwelling nasogastric tubes until they reached full oral feeding.
Interventions	Intervention group (N=40): Semi-demand feeding- infants received 10 minutes of non-nutritive sucking every three hours to assess wakefulness and behavioural state. Infants who were wakeful were offered an oral feed. If the infant was not sufficiently awake, he/she was left to sleep a further 30 minutes and the process was repeated. If the infant continued to sleep at that stage, (s)he was given a gavage feed of the full prescribed volume. Feeds were stopped when the infant stopped sucking or fell asleep or demonstrated clinically instability. If the minimum prescribed amount was not taken the infants were supplemented by gavage. Control infants (N=41) received prescribed volumes of milk either orally or via a feeding-tube at three hourly interval. Feeding duration was restricted to a maximum of 30 minutes. One infant in the control group was transferred to another hospital after completing the study protocol. The "age at discharge home" is not known.
Outcomes	Time taken from start of study to achieve full oral feeding, and rate of weight gain (grams per day) during transition from enteral tube to oral feeds.
Notes	Setting: Neonatal units affiliated to University of Cincinnati, Ohio, USA, late 1990s. Randomisation method: pre-prepared random sequence unknown to investigators (personal communication from principal investigator).

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Blinding of randomisation: yes
Allocation concealment?	Yes	Blinding of randomisation: yes
Blinding? All outcomes	No	Blinding of intervention: no Blinding of outcome measurement: no
Incomplete outcome data addressed? All outcomes	Yes	Complete follow-up: yes
Free of selective reporting?	Yes	

Free of other bias?	Yes	

Pridham 1999

Methods	Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	150 infants less than 35 weeks' gestational age at birth and appropriate weight for gestational age were enrolled and randomised. Infants were enrolled in the trial when taking at least 80% of enteral feeds directly from a nipple (either breast or bottle), at which point tube feeding was ceased and all feeds were offered by nipple. Most infants received standard formula milk. As part of a factorial trial design, some infants were randomly allocated to receive calorie-enriched formula milk.
Interventions	Intervention (N= 94): "*Ad libitum*" initiated response to infant hunger cues and terminated in response to infant satiation. Control (N= 56): Prescribed feeding at 4 hourly intervals.
Outcomes	Weight change and volume-and calorie-intake during the study period (5 days).
Notes	Setting: Level III neonatal unit in Wisconsin, USA. 1992- 1994. Further information on methodology kindly provided by trial investigators.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Blinding of randomisation: yes
Allocation concealment?	Yes	Blinding of randomisation: yes
Blinding? All outcomes	No	Blinding of intervention: no Blinding of outcome measurement: no
Incomplete outcome data addressed? All outcomes	No	Failure to complete full 5 days study period: 69 of the 150 (46%) enrolled infants were discharged home before completing the 5 days study period and no outcome data were presented for these infants.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Pridham 2001

Methods	Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	49 infants less than 35 weeks' gestational age at birth and appropriate weight for gestational age. Infants were enrolled in the trial when taking at least 80% of enteral feeds directly from a nipple (either breast or bottle), at which point tube feeding was ceased and all feeds were offered by nipple. Most participating infants received breast milk.
Interventions	Intervention (N= 25): "*Ad libitum*" initiated in response to infant hunger cues and terminated in response to infant satiation. Control (N= 24): Prescribed feeding at 3 hourly intervals.
Outcomes	Weight change and volume-and calorie-intake during the study period (5 days).
Notes	Setting: Level III neonatal unit in Wisconsin, USA. 1990- 1993. Further information on methodology kindly provided by trial investigators.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Blinding of randomisation: yes
Allocation concealment?	Yes	Blinding of randomisation: yes
Blinding? All outcomes	No	Blinding of intervention: no Blinding of outcome measurement: no
Incomplete outcome data addressed? All outcomes	No	Failure to complete full 5 days study period: 23 of the 49 (47%) enrolled infants were discharged home before completing the 5 days study period and no outcome data were presented for these infants.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Puckett 2008

Methods	Blinding of randomisation: no Blinding of intervention: no Complete follow-up: yes Blinding of outcome measurement: no
Participants	80* infants (including healthy moderately preterm infants and previously ventilated convalescing ELBW infants including those remaining oxygen dependent) with current weight >1500 g and tolerating full oral feeds were randomised at 32-36 weeks' postmenstrual age. Infants being mechanically ventilated and those with congenital abnormalities, major gastrointestinal surgery or severe intraventricular haemorrhage were excluded.
Interventions	Intervention (N=40): At study entry, gavage feeds were discontinued and infants fed orally on demand in response to hunger cues (crying, hand to mouth activity, finger/fist/pacifier sucking, rooting, persistently "unsettled" following a nappy change or repositioning). Five hours limit between feeds- if no cues the infant was woken for feeding. Control (N= 40): Continued standard scheduled (schedule not reported) gavage and bottle feeding. Both groups: "Breastfeedings were allowed as per parent's request". Type(s) of formula used were not reported. Modes of interim feeding other than gavage and bottle not reported.
Outcomes	Weight gain (g/kg/day), length of stay following enrolment, menstrual age at discharge, adverse events (apnoea and bradycardia) during feeding, number of cues per feed in the intervention group, and resource utilisation using nurse-patient ratios.
Notes	Setting: Level III neonatal unit in Saskatoon, Saskatchewan, Canada. 2001-2003. Data collected until hospital discharge are reported. *Outcome data were presented for 79 of the 80 randomised infants (data missing for one infant in the intervention group)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Blinding of randomisation: no - randomisation method: Coin toss with subsequent infant allocated to opposite group.
Allocation concealment?	No	Blinding of randomisation: no - randomisation method: Coin toss with subsequent infant allocated to opposite group.
Blinding? All outcomes	No	Blinding of intervention: no Blinding of outcome measurement: no
Incomplete outcome data addressed? All outcomes	Yes	Complete follow-up: yes

Free of selective reporting?	Yes	
Free of other bias?	Yes	

Saunders 1991

Methods	Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	29 preterm infants without major neurological or gastrointestinal disorders. Infants were enrolled when their weight was greater than 1500 grams and they were fully enterally fed with formula milk.
Interventions	Intervention (N= 15): "Demand" fed in response to hunger cues (crying, finger/fist sucking, rooting, persistently "unsettled" following a diaper change or re-positioning). Five hours limit between feeds. Control (N=14): Prescribed feeding of set volumes at 3 hourly intervals to achieve at least 120 ml/kg/day intake. Infants in either group who failed to take adequate amounts orally for two consecutive feeds were fed a prescribed volume (to achieve a daily intake of 120 ml/kg/day) via an intragastric feeding tube for the next feed.
Outcomes	Volume of milk ingested and rate of weight gain during the 6 days trial period. Length of hospitalisation.
Notes	Setting: Level III neonatal unit at the Women's Hospital, Greensbora, North Carolina, USA. We gratefully received further information on methodology and results from the trial investigator.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Blinding of randomisation: yes
Allocation concealment?	Yes	Blinding of randomisation: yes
Blinding? All outcomes	No	Blinding of intervention: no Blinding of outcome measurement: no
Incomplete outcome data addressed? All outcomes	No	Three infants were withdrawn from the study, one for withdrawal of parental consent, one because of infection, and one because of hypoglycaemia. It is not stated

Saunders 1991 (*Continued*)

		which feeding group these infants had been randomly allocated to.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Waber 1998

Methods	Blinding of randomisation: no Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	13 preterm infants born before 34 weeks' gestation, and appropriate for gestational age. Weight greater than 1500 grams, postmenstrual age greater than 32 weeks' at time of enrolment and fully enterally fed.
Interventions	Intervention (N=5): "Demand"; oral feeding (intragastric tubes removed) in response to hunger cues (crying, finger/hand/pacifier sucking, rooting, "unsettled"). The feeds were regarded as complete and ceased in response to infant satiation cues (refusal to suck and sleep). If infant did not demonstrate hunger cues within five hours of a previous feed, then infant gently aroused to a "feeding alert state". Control (N=5): Prescribed feeding of set volumes at 3-4 hourly intervals to achieve intake of 140 to 150 ml/kg/day.
Outcomes	Growth: average weight gain during trial period. Average volume of intake, and calorie and protein intake during trial period. No standard deviations given.
Notes	Setting: The Children's Regional Hospital, Camden, New Jersey, USA.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Blinding of randomisation: no - "coin-toss" for alternate infants, with allocation to opposite group for subsequently-enrolled infant.
Allocation concealment?	No	Blinding of randomisation: no - "coin-toss" for alternate infants, with allocation to opposite group for subsequently-enrolled infant.
Blinding? All outcomes	No	Blinding of intervention: no Blinding of outcome measurement: no

Waber 1998 (*Continued*)

Incomplete outcome data addressed? All outcomes	No	10 of 13 enrolled infants completed the trial, but the reasons for withdrawal/drop-out were not stated.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

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

Anderson 1990	This trial assessed the effect of a range of nipples for bottle feeding and for non-nutritive sucking but did not specifically assess *ad libitum* or demand/semi-demand feeding versus scheduled interval feeding. This study was reported only as book chapter.
Chang 2004	This is a two period crossover study comparing ad libitum feeding with 3 hourly scheduled interval feeding. Because this study design does not allow the collection of meaningful data on growth and time to hospital discharge, the primary outcomes of this review, the trial was not considered eligible for inclusion.
Horton 1952	This is an observational study of demand feeding in low birth weight infants.
Kirk 2007	This is an epoch-comparison studies using a historic control cohort.

DATA AND ANALYSES

Comparison 1. Ad libitum feeding versus scheduled interval feeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Growth: weight change during study period (grams per kilogram per day)	2	138	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-2.36, 0.56]
2 Postnatal age at discharge (days)	1	59	Mean Difference (IV, Fixed, 95% CI)	3.0 [-7.28, 13.28]
3 Postmenstrual age at discharge (weeks)	2	138	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.94, -0.01]
4 Time to establishment of full oral feeds (after trial entry)	1	59	Mean Difference (IV, Fixed, 95% CI)	-2.2 [-3.07, -1.33]
5 Nutrient intake during trial period (non breast fed infants only)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Volume of milk (millilitres per kilogram per day)	2	91	Mean Difference (IV, Fixed, 95% CI)	-7.41 [-16.86, 2.04]
5.2 Calorie intake (kilocalories per kilogram per day)	1	41	Mean Difference (IV, Fixed, 95% CI)	-20.0 [-32.61, -7.39]

Comparison 2. Demand/semi-demand feeding versus scheduled interval feeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Growth: weight gain during study period (grams per day)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Gavage to oral feeding transition phase	1	81	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-6.55, 0.95]
1.2 Exclusive oral feeding phase (first 48 hours)	1	81	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-7.41, 4.21]
2 Postmenstrual age at discharge (weeks)	1	80	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-0.97, -0.23]
3 Time to establishment of full oral feeds (days after trial entry)	1	81	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-6.61, -3.39]
4 Nutrient intake during the trial period (millilitres per day)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Gavage to oral feeding transition phase	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2 Exclusive oral feeding phase (first 48 hours)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Calorie intake during the trial period (per kilogram per day)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

5.1 Gavage to oral feeding transition phase	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.2 Exclusive oral feeding phase (first 48 hours)	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Ad libitum feeding versus scheduled interval feeding, Outcome 1 Growth: weight change during study period (grams per kilogram per day).

Review: Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants

Comparison: 1 Ad libitum feeding versus scheduled interval feeding

Outcome: 1 Growth: weight change during study period (grams per kilogram per day)

Study or subgroup	Ad libitum N	Mean(SD)	Scheduled interval N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kansas 2004	29	8.6 (5.3)	30	11.9 (6.1)		25.0 %	-3.30 [-6.21, -0.39]
Puckett 2008	39	12.6 (4.1)	40	12.7 (3.5)		75.0 %	-0.10 [-1.78, 1.58]
Total (95% CI)	**68**		**70**			**100.0 %**	**-0.90 [-2.36, 0.56]**

Heterogeneity: Chi^2 = 3.48, df = 1 (P = 0.06); I^2 =71%

Test for overall effect: Z = 1.21 (P = 0.23)

Analysis 1.2. Comparison 1 Ad libitum feeding versus scheduled interval feeding, Outcome 2 Postnatal age at discharge (days).

Review: Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants

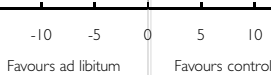
Comparison: 1 Ad libitum feeding versus scheduled interval feeding

Outcome: 2 Postnatal age at discharge (days)

Study or subgroup	Ad libitum N	Mean(SD)	Scheduled interval N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kansas 2004	29	45 (22)	30	42 (18)		100.0 %	3.00 [-7.28, 13.28]
Total (95% CI)	**29**		**30**			**100.0 %**	**3.00 [-7.28, 13.28]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.57 (P = 0.57)

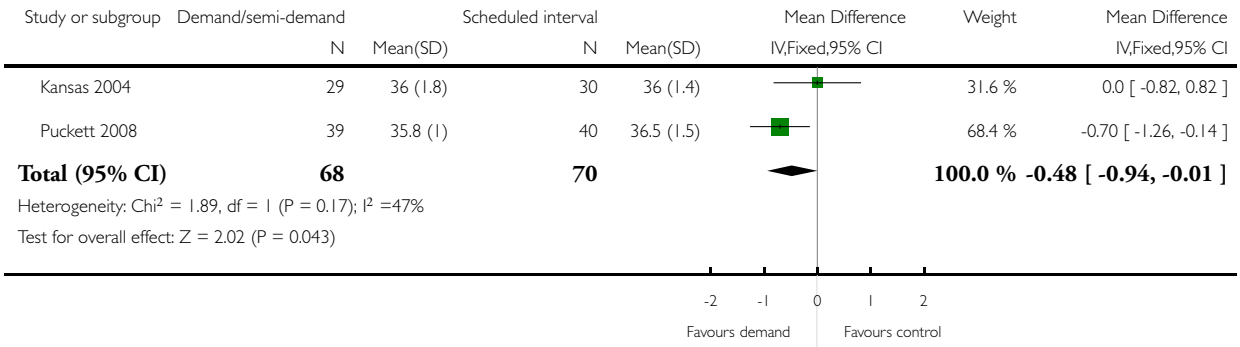


Analysis 1.3. Comparison 1 Ad libitum feeding versus scheduled interval feeding, Outcome 3 Postmenstrual age at discharge (weeks).

Review: Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants

Comparison: 1 Ad libitum feeding versus scheduled interval feeding

Outcome: 3 Postmenstrual age at discharge (weeks)

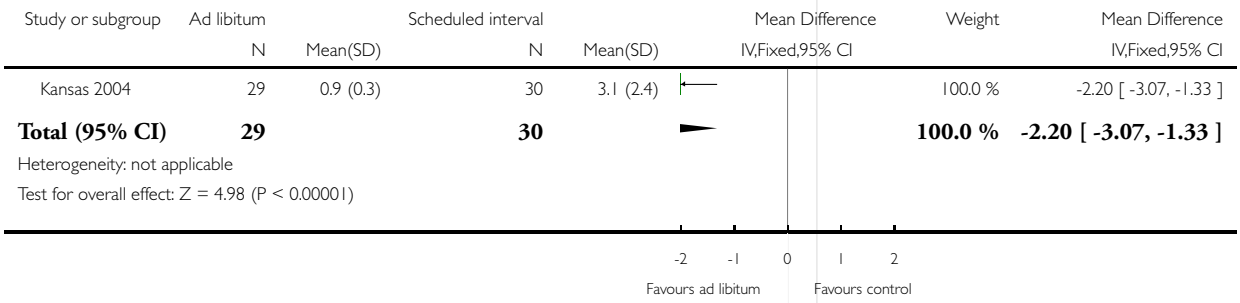


Analysis 1.4. Comparison 1 Ad libitum feeding versus scheduled interval feeding, Outcome 4 Time to establishment of full oral feeds (after trial entry).

Review: Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants

Comparison: 1 Ad libitum feeding versus scheduled interval feeding

Outcome: 4 Time to establishment of full oral feeds (after trial entry)

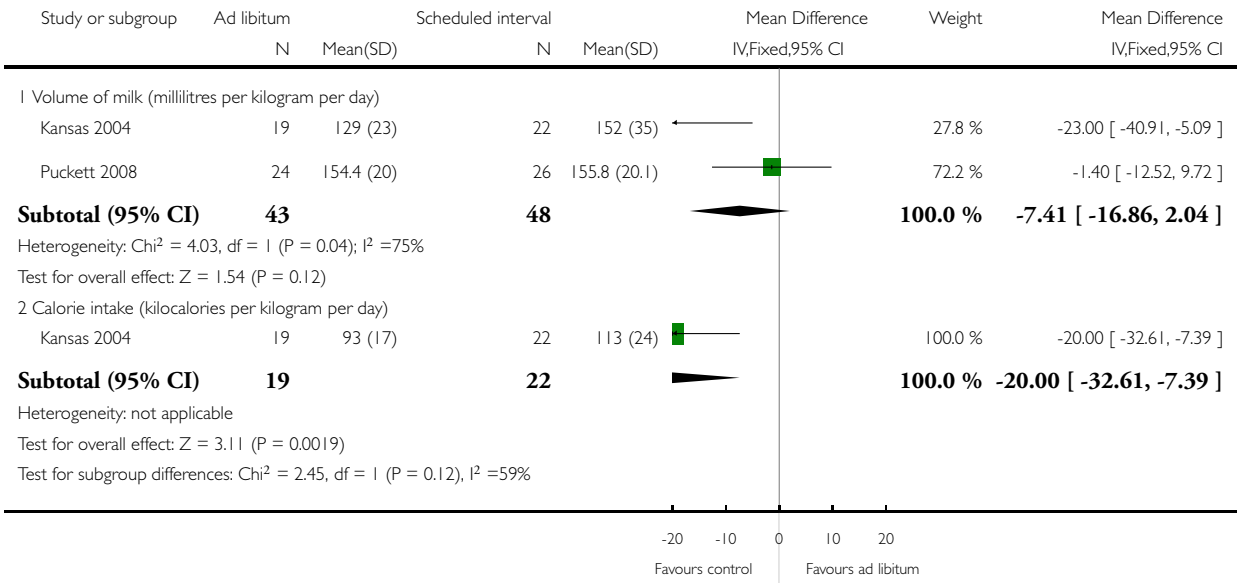


Analysis 1.5. Comparison 1 Ad libitum feeding versus scheduled interval feeding, Outcome 5 Nutrient intake during trial period (non breast fed infants only).

Review: Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants

Comparison: 1 Ad libitum feeding versus scheduled interval feeding

Outcome: 5 Nutrient intake during trial period (non breast fed infants only)

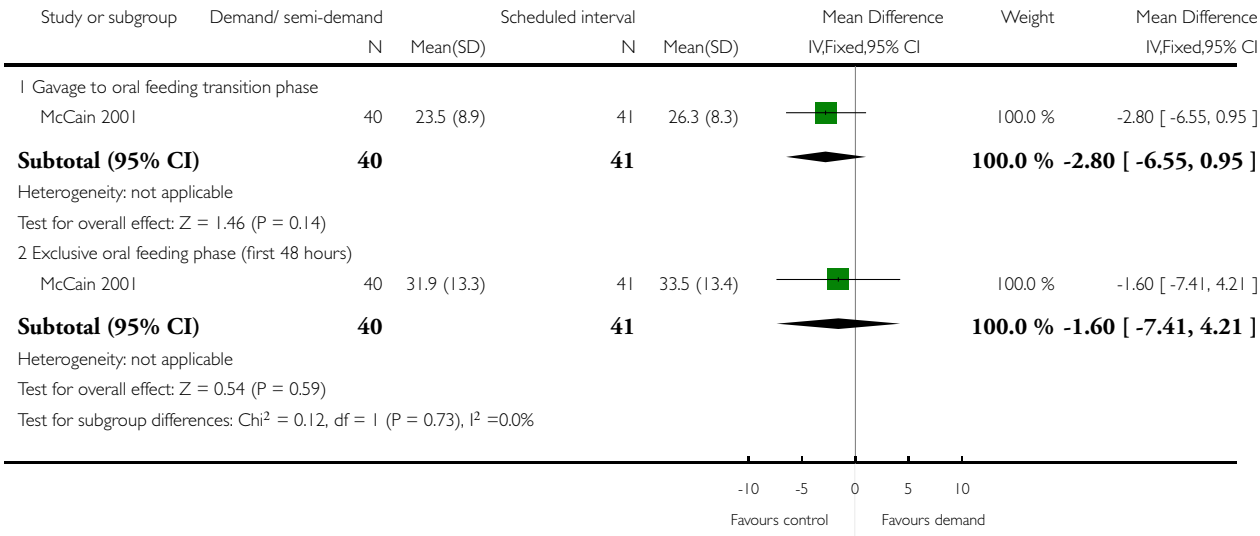


Analysis 2.1. Comparison 2 Demand/semi-demand feeding versus scheduled interval feeding, Outcome 1 Growth: weight gain during study period (grams per day).

Review: Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants

Comparison: 2 Demand/semi-demand feeding versus scheduled interval feeding

Outcome: 1 Growth: weight gain during study period (grams per day)

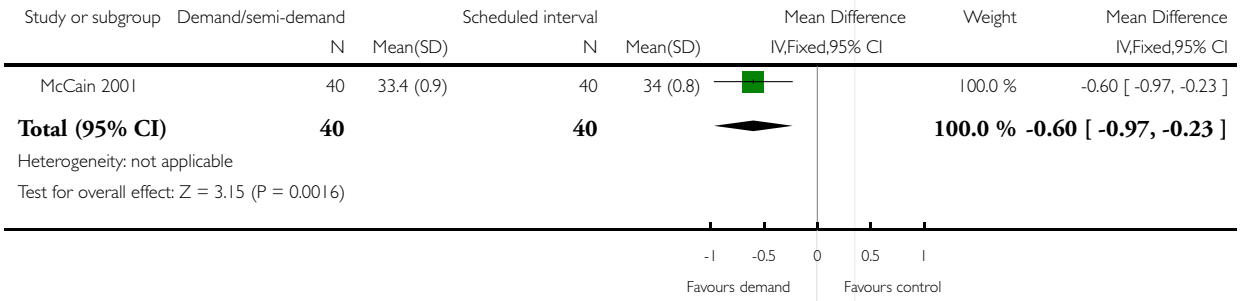


Analysis 2.2. Comparison 2 Demand/semi-demand feeding versus scheduled interval feeding, Outcome 2 Postmenstrual age at discharge (weeks).

Review: Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants

Comparison: 2 Demand/semi-demand feeding versus scheduled interval feeding

Outcome: 2 Postmenstrual age at discharge (weeks)



Analysis 2.3. Comparison 2 Demand/semi-demand feeding versus scheduled interval feeding, Outcome 3 Time to establishment of full oral feeds (days after trial entry).

Review: Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants

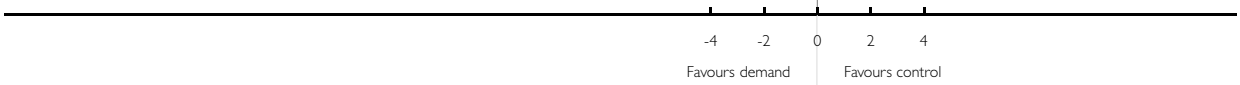
Comparison: 2 Demand/semi-demand feeding versus scheduled interval feeding

Outcome: 3 Time to establishment of full oral feeds (days after trial entry)

Study or subgroup	Demand/semi-demand N	Mean(SD)	Scheduled interval N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
McCain 2001	40	5 (4.2)	41	10 (3.1)	←	100.0 %	-5.00 [-6.61, -3.39]
Total (95% CI)	**40**		**41**		►	**100.0 %**	**-5.00 [-6.61, -3.39]**

Heterogeneity: not applicable

Test for overall effect: Z = 6.08 (P < 0.00001)



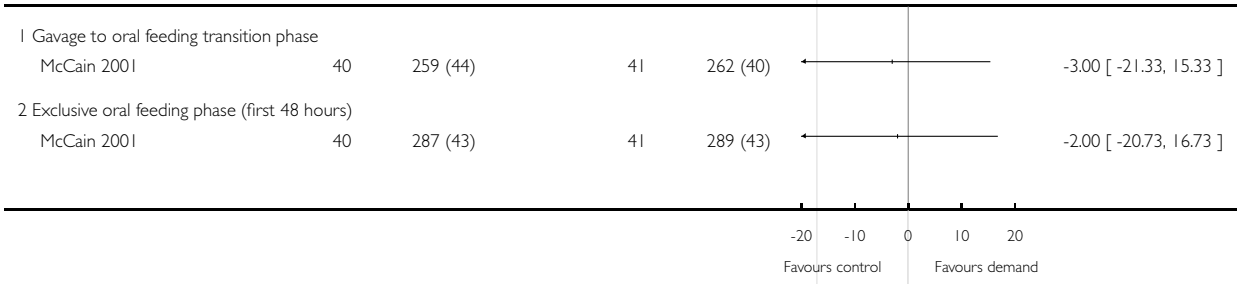
Analysis 2.4. Comparison 2 Demand/semi-demand feeding versus scheduled interval feeding, Outcome 4 Nutrient intake during the trial period (millilitres per day).

Review: Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants

Comparison: 2 Demand/semi-demand feeding versus scheduled interval feeding

Outcome: 4 Nutrient intake during the trial period (millilitres per day)

Study or subgroup	Demand/semi-demand N	Mean(SD)	Scheduled interval N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Gavage to oral feeding transition phase						
McCain 2001	40	259 (44)	41	262 (40)		-3.00 [-21.33, 15.33]
2 Exclusive oral feeding phase (first 48 hours)						
McCain 2001	40	287 (43)	41	289 (43)		-2.00 [-20.73, 16.73]



Analysis 2.5. Comparison 2 Demand/semi-demand feeding versus scheduled interval feeding, Outcome 5 Calorie intake during the trial period (per kilogram per day).

Review: Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants

Comparison: 2 Demand/semi-demand feeding versus scheduled interval feeding

Outcome: 5 Calorie intake during the trial period (per kilogram per day)

Study or subgroup	Demand/semi-demand N	Mean(SD)	Scheduled interval N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Gavage to oral feeding transition phase						
McCain 2001	40	122 (10)	41	118 (7)		4.00 [0.23, 7.77]
2 Exclusive oral feeding phase (first 48 hours)						
McCain 2001	40	126 (14)	40	119 (10)		7.00 [1.67, 12.33]

WHAT'S NEW

Last assessed as up-to-date: 22 December 2009.

31 October 2009	New citation required and conclusions have changed	Modified implications for practice and research. New author added to citation.
31 October 2009	New search has been performed	This updates the review "Ad libitum or demand/semi-demand feeding versus scheduled interval feeding for preterm infants" published in the Cochrane Database of Systematic Reviews, Issue 3, 2006 (Tosh 2006). The updated search identified one new study for inclusion (Puckett 2008). Following inclusion of data from this trial, we have modified the implications for practice and research to state that some limited evidence exists to suggest that *ad libitum* or demand/semi-demand feeding might reduce the duration of hospital admission in preterm infants and that further trials are needed to confirm or refute this suggestion.

HISTORY

Protocol first published: Issue 2, 2005

Review first published: Issue 3, 2006

24 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Karen Tosh (KT) and William McGuire (WM) developed the original protocol and undertook the original review (Tosh 2006).

For the 2009 update, WM screened the title and abstract of all studies identified by the search strategy.

WM and Felicia McCormick (FM) screened the full text of the report identified as of potential relevance, assessed the methodological quality of the included trials, extracted the relevant information and data, and completed the final updated review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- CRD, HYMS, University of York, UK.
- University of St Andrews, UK.
- Department of Health Sciences, University of York, UK.

External sources

- Tenovus Scotland, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Enteral Nutrition [*methods; standards]; Hunger [physiology]; Infant, Newborn; Infant, Premature [*physiology]; Infant Nutritional Physiological Phenomena [*physiology]; Randomized Controlled Trials as Topic; Satiation [physiology]; Time Factors

MeSH check words

Humans