

Three-Hourly versus Two-Hourly Feeding Interval in Stable Preterm Infants: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Research Article

Keywords: Feed Intolerance, Infants, Necrotizing enterocolitis, Nutrition, Small for gestational age

Posted Date: September 20th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-888420/v1>

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Version of Record: A version of this preprint was published at European Journal of Pediatrics on February 11th, 2022. See the published version at <https://doi.org/10.1007/s00431-022-04405-y>.

Abstract

Evidence from randomized controlled trials (RCTs) suggests that three-hourly feeding is safe and might help achieve full feeds earlier in preterm infants. We systematically compared the benefits and harms of three-hourly and two-hourly feeding schedules in preterm infants. We searched electronic databases (MEDLINE, CINAHL, Embase, Web of Science, and Scopus) and trial registries until 30 July 2021 for RCTs comparing the two feeding schedules. We did random-effects meta-analysis using RevMan 5.4 software. The primary outcome was the incidence of stage II or III necrotizing enterocolitis (NEC). Other outcomes were the incidence of any stage NEC, sepsis, mortality, time to full enteral feeds, and hospital stay. Six trials (872 participants) are included. There was no significant difference in the incidence of stage II/III NEC (3 trials; 530 participants; RR 1.39; 95% CI: 0.53,3.65; I^2 -0%, low certainty), and any stage NEC (5 studies; 767 participants; RR 0.98; 95% CI: 0.53,1.82; I^2 0%, very-low certainty) between three and two-hourly feeding groups. There was no difference in the time to achieve full feeds (5 trials; 755 participants; MD: -0.0 days; 95% CI: -0.32, 0.31, low certainty) or other outcomes. On subgroup analysis, neonates with birthweight <1000 grams and in the three-hourly feeding regime achieved full enteral feeds slower than those in the two-hourly feeding group (1 trial; 84 participants; MD: 2.9 days, 95% CI: 1.16, 4.64, low certainty).

Conclusion

In stable preterm infants (1000-1500 grams), three-hourly feeding can be followed safely. In infants <1000 grams, two-hourly feeding should be continued till further evidence.

Prospero Registration Number: CRD42021246568

What Is Known

- Most of the units follow two hourly feeding schedules without any evidence.
- Recent trials suggest that the three hourly feeding schedules can be safely followed in stable preterm infants.

What Is New

- Low certainty evidence suggest that three-hourly feeding is safe in stable preterm infants (1000–1500 grams).
- In infants < 1000 grams, two-hourly feeding should be continued as it helps in achieving full feeds earlier.

Introduction

Bolus feeding is considered more physiological than continuous feeding in preterm infants [1, 2]. As a convention, most units prescribe enteral feeding at an arbitrary interval of two hours irrespective of the infant's weight or physiological maturity and continue the same until demand breastfeeding is achieved [3, 4]. A short interval (1–2 hour) feeding schedule delivers a smaller volume per feed that may be more easily tolerated. However, frequent bolus feeding might lead to persistently high superior mesenteric artery blood flow, which might not be physiological [5]. Also, frequent feeding stresses nurses (frequent feed administration), mothers (frequent milk expression leading to reduced rest time), and infants (less sleep, shorter Kangaroo mother care duration) [3].

On the other hand, a longer feeding interval (3 hours or more) translates to a higher volume per feed, which might not be well-tolerated in extremely preterm infants. However, longer feeding intervals might improve postprandial blood flow, gut motility, and help achieve full enteral feeds earlier [5]. It might have an impact on reducing nursing time spent on feeding and improving mother-infant attachment.

Due to the lack of scientific basis for a two-hourly feeding schedule and perceived advantages of extended feeding schedules, three hourly feedings have been used successfully without any adverse effects [6–8]. Some studies observed that three hourly feeding schedules might help achieve full enteral feeds earlier, therefore, decreasing the duration of parenteral nutrition and central venous catheter [6]. A previous systematic review concluded that low-quality evidence shows that the three-hourly feeding schedule is safe and helps regain birth weight earlier than a 2-hourly feeding schedule [9]. However, these conclusions are limited by the small sample size and failed to change the clinical practice, thereby merit further exploration [10]. Moreover, these results were limited to achieving full gavage feeds and did not assess the impact on the further transition to oral feeds and time to discharge. Recently a few more studies comparing the two feeding schedules have been published [11, 12], warranting a systematic relook into the evidence.

We aimed to systematically synthesize the evidence on clinical benefits and harms associated with a three-hourly feeding schedule compared to a conventional two-hourly feeding schedule in stable preterm infants.

Material And Methods

Search strategy

We followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines [13] and Cochrane Handbook for Systematic Reviews of Interventions [14]. The protocol was prospectively registered with PROSPERO (CRD42021246568). We searched Medline (by PubMed), Embase, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), *Cumulative Index to Nursing and Allied Health Literature* (CINAHL), and Scopus for randomized controlled trials (RCTs) published until July 30, 2021. One author (JK) developed the electronic search strategy for individual databases (Supplementary Table S1), which was later independently peer-reviewed by two different

authors (JM, PD) using the Peer Review of Electronic Search Strategies (PRESS) checklist [15]. After finalizing the search strategy, two investigators (JK, JM) independently searched the literature using the database-specific subject headings (MeSH/Emtree terms), keywords, free-text, and word variants for the study population (Preterm Infants), intervention (Three hourly feeding schedule), control (Two-hourly feeding schedule), and study design (RCT). The electronic database search was supplemented by a manual search of the bibliography of the relevant guidelines, reviews and included studies. We also searched various clinical trial registries, namely Clinical Trial Registry India (CTRI), ClinicalTrials.gov, and EU Clinical Trials Register (<https://www.clinicaltrialsregister.eu>), to identify additional published records (searched on July 30, 2021). We did not use any language restriction, limits, or filters in the literature search.

Study selection

RCTs comparing a three-hourly feeding schedule with a two-hourly feeding schedule among preterm infants (< 37 weeks) were considered eligible for this systematic review. First, two investigators (JK, JM) independently screened the titles and abstracts for eligibility and identified potentially eligible studies for full-text screening. Later, two different authors (JK, PD) independently examined the full text of the above-identified studies and included them in the review if they met all the following criteria: (i) Population-Stable preterm (< 37 weeks) infants on gavage/spoon/paladai/cup feeds and admitted in hospital (ii) Intervention- Three-hourly feeding schedule, (iii) Comparison- Two-hourly feeding schedule, (iv) Outcome-reported one or more of the predefined clinical outcomes (mentioned below), and (iv) study design- RCT only. We excluded studies including (i) term infants or older children, (ii) infants on direct breastfeeds or demand feeding, (iii) infants with structural malformations or surgical gastrointestinal anomalies; studies (iv) comparing other feeding intervals, and (v) not reporting any of the predefined clinical outcomes.

Primary and Secondary outcomes

Our primary outcome was the incidence of necrotizing enterocolitis (NEC) \geq stage 2 as per modified Bell's staging. The secondary outcomes included incidence of any stage NEC, time to reach full enteral feeds (at least 100 mL/kg/day), time to reach full oral (cup/spoon/paladai) feeds, time to regain birth weight, rate of weight gain (g/kg/day), time to discharge, the incidence of culture-proven or/and clinical sepsis (as defined by primary authors), number of days of total parenteral nutrition (TPN) and central venous catheter (CVC) usage, number of episodes of feed intolerance, all-cause in-hospital mortality, and anthropometry parameters (weight/length/ occipitofrontal circumference) at discharge, 40- weeks post-menstrual age, and follow-up.

Data extraction and quality assessment

Two investigators (JM, JK) read the full text of all included studies and independently extracted the study data using a predesigned structured performa. The extracted data included, but was not limited to, the first author's name, year of publication, inclusion and exclusion criteria, study design, and methodology (randomization, allocation concealment, blinding, attrition, protocol deviations, etc.) to assess the risk of bias, demographic details of the study participants of each group, feeding protocol (type of feeds, rate of

feed hiking, mode of feeding, TPN details) and predefined clinical outcomes. This data was later entered into RevMan version 5.3 software for analysis. Another investigator (PD) cross-checked the entire extracted data for its completeness and accuracy. Two investigators (JK and JM) independently assessed the risk of bias using the Cochrane collaboration tool [16]. A senior investigator (PK) intervened in case of disagreement, and his decision was considered final. We also contacted the corresponding authors of the included studies for additional details and included them in the analysis. Studies with multiple published reports were combined and summarized under the primary study as per PRISMA 2020 recommendations [13].

Statistical analysis

We systematically synthesized evidence for all predefined outcomes. Considering the variability in the study population and feeding protocols, we used random-effects meta-analysis. We calculated the pooled risk ratio (RR) for dichotomous variables and mean difference (MD) for continuous variables, along with 95% confidence intervals (CI). RevMan calculator or appropriate statistical conversion formulas were used to convert interquartile range (IQR), range, or 95% CI to standard deviation [17]. Study heterogeneity was explored by visual assessment of the forest plots and Chi-square test on Cochrane's Q statistics and was quantified with I^2 statistics. As decided *a priori*, we did subgroup analysis based upon gestational age, birth weight, and intrauterine growth restriction status, wherever feasible. We also did sensitivity analysis to explore the heterogeneity. RevMan 5.3 software was used for quantitative analysis.

We followed standard GRADE recommendations to assess the certainty of the evidence for the clinical outcomes and used GRADE Pro software (<https://gdt.gradepro.org>) to generate the summary of findings table [18, 19]. Two researchers (JK, JM) independently assessed the certainty of the evidence, and the discrepancy was resolved through discussion with an experienced researcher (PK).

Results

A total of 2989 records were identified, of which 357 duplicates were removed before the screening. We screened through titles and/or abstracts of 2612 articles, of which 23 were considered potentially relevant for full-text screening. Out of 23, six reports [11, 12, 20–23] fulfilled the inclusion criteria and were evaluated for qualitative and quantitative synthesis (Fig. 1). We identified one additional study through citation search [8]. Two published reports [12, 23] from one trial were combined under the primary research for analysis. The exact reasons for excluding full-text articles are given in Fig. 1. Details of excluded studies are provided in the supplementary appendix.

Study Characteristics and Risk of Bias Assessment

Six studies (872 participants) are included in this systematic review [8, 11, 12, 20–22]. The mean gestation varied between 30–32 weeks across the trials. About one-third of the total enrolled neonates were small for gestational age (SGA). All except one included very low-birthweight (< 1500 grams) neonates. Dhingra et al. enrolled neonates up to 1750 grams [20], though most were very low birth weight

only (mean birth weight was 1210 g and 1249 grams in three and two-hourly feeding groups, respectively). Detailed descriptions of the study participants, eligibility criteria, feeding schedule, and outcomes are provided in Table 1. We used the Cochrane Collaboration tool for assessing the risk of bias of the randomized controlled trials [16]. All trials were open-label trials and were at high risk for performance bias. In addition, due to the nature of the intervention, blinding of outcome assessment was not possible, thus subjecting them to increased risk for detection bias for the subjective outcomes like feed intolerance, time to full enteral feeds, clinical sepsis, withholding feeds, and time to discharge (Fig. 1).

Table 1
Characteristics of the Included Studies

Author (Year)	Inclusion and Exclusion Criteria	Study Participant Characteristics*		Feeding Protocol	Outcomes
		Three- hourly	Two- hourly		
Yadav A et al. (2021)	<p><i>Inclusion:</i> 1000–1500 g started on feeds within 96 hrs of life</p> <p><i>Exclusion:</i> Major CMF, severe perinatal asphyxia, severe illness, A/REDF in antenatal doppler.</p>	n-175 GA-32.5 (2.3) BW- 1310 (150) SGA- 74 (42%)	n-175 GA-32.3 (2.3) BW- 1320 (140) SGA- 65 (37%)	Feeding schedule: 1000–1250 gms: Start volume: 30 mL/kg/d. advancement rate: 30 mL/kg/d. >1250 gms: Full enteral feeds from day 1. Mode of feeding: Gavage or Cup/paladai. Type of feeds: EBM (85%), Preterm Formula (15%). Parenteral nutrition: Received intravenous fluids until enteral feed reached 120 mL/kg/d.	Time to full enteral feeds (150 mL/kg/d), NEC (stage \geq II), feed intolerance, hypoglycemia, etc.

Abbreviations: A/REDF- Absent/Reduced End Diastolic Flow; BW- Birth weight; CMF- Congenital Malformation; EBM: Expressed Breast Milk; ELBW- Extremely Low Birth Weight; GA- Gestational Age; LBW- Low Birth weight; NEC- Necrotising enterocolitis; SGA- Small for gestational age.

*n- number of participants, GA is expressed in weeks and BW in grams. GA and BW are presented as Mean (SD) unless specified.

Author (Year)	Inclusion and Exclusion Criteria	Study Participant Characteristics*		Feeding Protocol	Outcomes
		Three- hourly	Two- hourly		
Unal S et al. (2019)	<p>Inclusion: Neonates weighing < 1500 g and < 32 weeks. Randomized on achieving 1500 g weight and full gavage feeding (150 mL/kg/d). (no. of ELBW not provided)</p> <p>Exclusion: Major CMF, severe illness, perinatal asphyxia, respiratory support, and formula feeding >50%.</p>	n-50 GA- 29 (2.2) BW- 1153 (281)	n-50 GA- 29 (2.2) BW- 1228 (233)	<p>Feeding schedule: Before randomization: Start: 10 mL/kg/d; advancement rate: 20–30 mL/kg/d. Every 2 hourly</p> <p>After randomization: Start At least two oral feeds per day; advancement rate: as decided by nurses.</p>	Time to full oral feeds (150 mL/kg/d), duration of feeding transition, weight gain, hospital stay, weight at discharge.
Anushree MN et al. (2018)	<p>Inclusion: Neonates weighing < 1500 g (2 in each group were ELBW)</p> <p>Exclusion: Major CMF</p>	n-30 SGA- 4 (13.3%)	n-30 SGA- 6 (20%)	<p>Feeding schedule: Start volume: Not mentioned; advancement rate: 20mL/kg/d</p> <p>Type of feeds: EBM or LBW formula.</p> <p>Parenteral nutrition: Details not given</p>	Time to full enteral feeds (150 mL/kg/d), NEC (\geq stage II), feed intolerance, hypoglycemia, apnea.

Abbreviations: A/REDF- Absent/Reduced End Diastolic Flow; BW- Birth weight; CMF- Congenital Malformation; EBM: Expressed Breast Milk; ELBW- Extremely Low Birth Weight; GA- Gestational Age; LBW- Low Birth weight; NEC- Necrotising enterocolitis; SGA- Small for gestational age.

*n- number of participants, GA is expressed in weeks and BW in grams. GA and BW are presented as Mean (SD) unless specified.

Author (Year)	Inclusion and Exclusion Criteria	Study Participant Characteristics*		Feeding Protocol	Outcomes
		Three- hourly	Two- hourly		
Ibrahim NR et al. (2017)	<p><i>Inclusion:</i> <35 weeks and 1000–1500 g</p> <p>Started on feeds within 96 hrs of life.</p> <p><i>Exclusion:</i> Major CMF, perinatal asphyxia</p>	n-75 GA-30.9 (2.2) BW- 1300 (130) SGA- 20 (27%)	n-75 GA-30.4 (2.3) BW- 1270 (150) SGA-17 (23%)	<p>Feeding schedule: Start volume: 10–20 mL/kg/d; advancement rate: 10–20mL/kg/d</p> <p>Type of feeds: EBM (~ 40 %), Preterm formula.</p> <p>Parenteral nutrition: Start 10% dextrose or parenteral nutrition at 60–80 mL/kg/d. Increase by 15–20 mL/kg/d to reach 140–160 mL/kg/day and discontinue once enteral feed of 100 mL/kg/day is achieved.</p>	<p>Time to full enteral feeds (100 mL/kg/d), NEC, feed intolerance, apnea, sepsis, gastro-oesophageal reflux, time to regain birth weight.</p>
Tali SH et al. (2016)	<p><i>Inclusion:</i> Neonates weighing 501–1500 g (42 in each group were ELBW)</p> <p><i>Exclusion:</i> Major CMF, severe sepsis, grade III/IV intraventricular hemorrhage.</p>	n-60 GA- 30.5 (2.7) BW- 1139 (225) SGA- 14 (23%) A/REDF- 10 (17%)	n-60 GA- 30.1 (2.8) BW- 1176 (249) SGA- 12 (20%) A/REDF- 12 (20%)	<p>Feeding schedule: Start volume: 20 mL/kg/d; advancement rate: 20mL/kg/d</p> <p>Type of feeds: Preterm formula and EBM.</p> <p>Parenteral nutrition: details not given.</p>	<p>Time to full enteral feeds (150 mL/kg/d), NEC (all stages), feed intolerance, hypoglycemia, sepsis, mortality, time to attain BW, time to discharge, anthropometry at discharge, nursing time spent on feeding.</p>

Abbreviations: A/REDF- Absent/Reduced End Diastolic Flow; BW- Birth weight; CMF- Congenital Malformation; EBM: Expressed Breast Milk; ELBW- Extremely Low Birth Weight; GA- Gestational Age; LBW- Low Birth weight; NEC- Necrotising enterocolitis; SGA- Small for gestational age.

*n- number of participants, GA is expressed in weeks and BW in grams. GA and BW are presented as Mean (SD) unless specified.

Author (Year)	Inclusion and Exclusion Criteria	Study Participant Characteristics*		Feeding Protocol	Outcomes
		Three- hourly	Two- hourly		
Dhingra A et al. (2009)	<p><i>Inclusion:</i> Up to 1750 g (Total 11 were ELBW) on hiking feeds</p> <p><i>Exclusion:</i> Major CMF, severe illness, getting aminophylline/cisapride.</p>	n-46 GA-30.9 (2.1) BW- 1210 (249) SGA- 7 (16%)	n-46 GA-31.6 (2.3) BW- 1249 (250) SGA- 7 (16%)	Feeding Schedule: Not mentioned Type of feeds: EBM and LBW formula Parenteral nutrition: details not given.	Time to full enteral feeds (150 mL/kg/d), NEC, feed intolerance, hypoglycemia, apnea, sepsis, mortality, time to attain birth weight, time to discharge, nursing time spent on feeding.

Abbreviations: A/REDF- Absent/Reduced End Diastolic Flow; BW- Birth weight; CMF- Congenital Malformation; EBM: Expressed Breast Milk; ELBW- Extremely Low Birth Weight; GA- Gestational Age; LBW- Low Birth weight; NEC- Necrotising enterocolitis; SGA- Small for gestational age.

*n- number of participants, GA is expressed in weeks and BW in grams. GA and BW are presented as Mean (SD) unless specified.

Primary Outcome (Fig. 3a)

Our primary outcome was the incidence of NEC \geq stage 2 as per Modified Bell's staging. Three trials (530 participants) reported the primary outcome and did not find any statistically significant difference between the two groups (RR: 1.39; 95% CI: 0.53 to 3.65; $I^2=0\%$). Also, the incidence of any stage NEC did not differ significantly (5 studies, 767 participants, RR 0.98; 95% CI: 0.53 to 1.82, $I^2=0\%$) (Table 2).

Table 2
Comparison of Secondary Outcomes (Three-hourly vs. Two-hourly feeding Schedule)

Outcome	No. of studies (Participants)	RR/ MD [95% CI]	Heterogeneity (I^2), p-value	Certainty of the evidence
Necrotizing enterocolitis (Any stage)	5 (767)	0.98 [0.53, 1.82]	0%, 0.6	⊕ ● ● ● Very Low
Time to reach full enteral feeds (days)	5 (755)	-0.00 [-0.32, 0.31]	0%, 0.6	⊕ ⊕ ● ● Low
Culture-Positive Sepsis	2 (470)	1.02 [0.47, 2.19]	20%, 0.3	⊕ ⊕ ● ● Low
Any Sepsis	4 (707)	1.15 [0.77, 1.71]	0%, 0.6	⊕ ⊕ ● ● Low
All-cause mortality	2 (500)	1.31 [0.46, 3.76]	0%, 0.5	⊕ ⊕ ● ● Low
Duration of Hospital stay (days)	3 (307)	0.94 [-3.38, 5.26]	0%, 0.4	⊕ ⊕ ● ● Low
Time to regain birth weight (days)	4 (694)	-0.51 [-1.58, 0.55]	56%, 0.08	⊕ ⊕ ● ● Low
Weight at discharge (grams)	1 (87)	-57 [-244, 130]	Not applicable	⊕ ⊕ ⊕ ● Moderate
Weight gain after randomization (g/kg/day)	1 (100)	1.60 [0.22, 2.98]	Not applicable	⊕ ⊕ ● ● Low
Duration of intravenous fluid (days)	1 (87)	-0.40 [-2.12, 1.32]	Not applicable	⊕ ● ● ● Very Low
Nursing time spent (in minutes) on feeding (per Infant per day)	1 (87)	-22.0 [-23.9, -20.1]	Not applicable	⊕ ● ● ● Very Low
Time to reach full oral feeds (days)	1 (100)	2.00 [-4.70, 8.70]	Not applicable	⊕ ⊕ ● ● Low

Abbreviations: CI: Confidence interval; RR: Risk ratio; MD: Mean difference; GER- Gastroesophageal reflux

Outcome	No. of studies (Participants)	RR/ MD [95% CI]	Heterogeneity (I^2), p-value	Certainty of the evidence
Duration of transition from tube feeds to full oral feeds (days)	1 (100)	1.00 [-1.03, 3.03]	Not applicable	⊕⊕●● Low
Adverse Effects				
Feed intolerance	6 (867)	0.94 [0.71, 1.24]	0%, 0.7	⊕⊕●● Low
GER requiring medication	2 (237)	1.14 [0.48, 2.70]	1%, 0.3	⊕●●● Very Low
Hypoglycemia	5 (767)	1.13 [0.63, 2.01]	0%, 0.9	⊕⊕⊕● Moderate
Apnea	3 (267)	0.87 [0.49, 1.54]	0%, 0.7	⊕⊕●● Low

Abbreviations: CI: Confidence interval; RR: Risk ratio; MD: Mean difference; GER- Gastroesophageal reflux

Secondary Outcomes

Considering the variability in the definition of full enteral feeds, we defined a volume of at least 100 mL/kg/day as full enteral feeds. However, we also compared the time to reach full enteral feeds for different thresholds (Table 2). There was no significant difference in time to achieve full enteral feeds between the two schedules (5 trials, 755 participants, MD: -0.0 days, 95% CI: -0.32, 0.31; $I^2=0\%$). However, irrespective of the definition used, the two groups achieved full feeds simultaneously (Fig. 3b).

There was no significant difference between the groups in the incidence of sepsis (culture-positive or clinical), all cause-mortality, duration of hospital stays, daily weight gain (g/kg/day), time to regain birth weight, weight at discharge, duration of intravenous fluids, and length of hospitalization (Table 2). In addition, there was no significant difference in the incidence of hypoglycemia, apnea, feed intolerance, or GER requiring medical therapy between the two feeding schedules (Table 2).

Three hourly feeding schedules were associated with a shorter duration of nursing time spent on feeding (1 trial, 87 participants, MD -22.00 minutes/day, 95% CI -23.9 to -20.1 minutes/day). However, one trial [11] also compared the time to reach full oral feeding and time taken for transitioning from tube to oral feeding and did not observe any significant differences (Table 2).

None of the trials reported TPN duration, CVC duration, anthropometry at 40 weeks, or during follow-up.

Sub-group analysis

As decided a priori, subgroup analysis was performed to assess the effect of birth weight, gestation, and small for gestational age (SGA) status.

Birth weight (Extremely low birth weight Infants)

Five trials (772 participants) reported enrollment of 99 (12.8%) extremely low birth weight (ELBW) neonates. However, only one trial (84 ELBW) reported the outcomes in this subgroup. This trial did not report data on NEC; however, they showed that ELBW neonates fed three-hourly achieved full enteral feeds (150 mL/kg/d) slower than those fed at two-hourly intervals (14.14 vs. 11.24 days; MD: 2.90 days, 95% CI: 1.16 to 4.64, p=0.04). There was no difference in feed intolerance, apnea, and hypoglycemia among the two groups. As the other four trials enrolled only 15 ELBW neonates (2.3% of all participants), the results are unlikely to be affected by the missing outcome information.

Small for gestational Age

Out of 872 participants, 245 (28.1%) were SGA; however, only two trials (166 participants) provided separate data on outcomes in them. There was no significant difference in NEC (stage 2 or more), feed intolerance, hypoglycemia, time to full enteral feeds, and time to regain birth weight between the two feeding schedules amongst SGA infants (Table 3).

Table 3
Subgroup analysis (Three-hourly vs. Two-hourly feeding Schedule)

Outcome	No. of studies (Participants)	RR/ MD [95% CI]	Certainty of the evidence
Small for Gestational Age Neonates			
Necrotizing enterocolitis (Stage 2 or more)	1 (139)	0.66 [0.15, 2.83]	⊕⊕●● Low
All-cause mortality	1 (139)	1.32 [0.23, 7.64]	⊕⊕●● Low
Time to reach full enteral feeds (days)	2 (166)	-0.31 [-1.98, 1.35]	⊕●●● Very Low
Time to regain birth weight (days)	2 (166)	-0.83 [-5.60, 3.94]	⊕⊕●● Low
Feed intolerance	1 (139)	1.23 [0.41, 3.69]	⊕●●● Very Low
Hypoglycemia	1 (139)	1.76 [0.33, 9.28]	⊕⊕●● Low
Birth Weight (501–1000 grams)			
Time to reach full enteral feeds (days)	1 (84)	2.90 [1.16, 4.64]	⊕⊕●● Low
Feed Intolerance	1 (84)	1.44 [0.69, 3.01]	⊕●●● Very Low
Apnea	1 (84)	3.00 [0.13, 71.61]	⊕●●● Very Low
Hypoglycemia	1 (84)	1.00 [0.06, 15.47]	⊕●●● Very Low
Abbreviations: CI: Confidence interval; RR: Risk ratio; MD: Mean difference			

None of the trials provides separate data for variables like gestational age, type of feeds (formula/human milk), probiotics use, and antenatal doppler abnormalities (absent/reversed end-diastolic flow), which can potentially affect the outcomes [24, 25]. Therefore, we could not do subgroup analysis for these variables.

Due to fewer trials, we could not do meta-regression to assess the effect of gestational age birth weight on various outcomes; or identify meaningful subgroup interaction effect.

Sensitivity Analysis

We also did a fixed-effect meta-analysis, but the results were almost similar for all outcomes (Supplementary Table S2). There was no significant heterogeneity for any outcome except time to regain birth weight ($I^2=56\%$, $p=0.08$). Finally, we did a sensitivity analysis to explore this heterogeneity and observed that the heterogeneity is mainly contributed by Yadav et al.'s study [12]. In this trial, the mean gestational age, birth weight, and proportion of SGA neonates were higher than others. After excluding this study, the pooled analysis of 3 studies (350 participants) showed that the infants in the three hourly feeding group regained birth weight earlier than the two-hourly feeding group (MD -1.11 days; 95% CI -2.16 to -0.06 days; $I^2=0\%$). As most neonates in the Tali et al. study (22) were ELBW, and the authors provided separate data for some outcomes, we did sensitivity analysis by excluding the ELBW population. The effect size and direction were similar for all results, though the confidence interval widened due to the loss of sample size. We intended to assess publication bias using the funnel plot and Egger's test; however, we could not do it due to a small number of studies ($n < 10$).

Discussion

In this systematic review of six RCTs, three hourly feedings were not associated with an increased incidence of NEC (stage 2 or more) or all-cause mortality compared to two-hourly feeding in stable preterm infants (low certainty evidence). In addition, the time to reach full enteral feeds, duration of hospitalization, the incidence of sepsis, and anthropometric parameters at discharge in the three hourly feeding group were not different from the two-hourly feeding group (low to moderate certainty evidence). The incidence of feed intolerance, regurgitation of feeds, and apnea were also similar (low to very low certainty evidence). Furthermore, the moderate certainty evidence suggests that the risk for hypoglycemia with three hourly feeding schedules is not different from a two-hourly feeding schedule. In addition, a three-hourly plan saved the nursing time spent on feeding (very low certainty evidence).

On subgroup analysis, three hourly feedings were safe in SGA neonates, who are at a higher risk for NEC, feed intolerance, and hypoglycemia (low to very-low certainty evidence). Based on a single small trial, three hourly feedings were safe in ELBW neonates (500–1000 grams) but took longer to reach full enteral feeds (low to very-low certainty evidence).

As 85% of the study population was between 1000–1500 grams, these results can be generalized to this birth weight group. However, the safety data in ELBW neonates was based on a single small trial. Therefore, due to the small sample size and wider confidence intervals, we are uncertain about the outcomes in this subpopulation. Moreover, two hourly feeding schedules helped achieve full feeds earlier in the ELBW infants, though the evidence is low-quality. Therefore, a two-hourly feeding schedule may be followed in ELBW infants until more evidence is available.

There is marked variability in feeding practices among neonatal units across the world [26]. Most neonatal units' practice two-hourly feeding schedules for stable preterm infants. This practice of two-hourly feeding is based on tradition rather than evidence. Two hourly feeding increases the nursing workload and involves more frequent handling of the neonates, which might be stressful [3, 20]. Physiologically, frequent bolus feeding is not desirable as it leads to persistently increased superior mesenteric artery blood flow [5, 10].

Previous observational studies showed variable results precluding meaningful conclusions [6, 7, 27]. Initial small RCTs suggested three hourly feedings can be safely followed in stable very-low birth weight infants [20, 21]. Based on limited evidence, Dutta et al. suggested using three hourly feedings in infants weighing > 1250 grams; however, they advised continuing a 2-hourly schedule for infants < 1250 grams [4]. On the other hand, with the same evidence, Binchy et al. suggested 2-hourly feeding in all VLBW infants [3]. World health organization feeding guidelines advocate bolus feeding over continuous feeding but do not recommend any feeding interval [28]. To some extent, these conflicting recommendations are a result of the pooling of heterogeneous observational studies. Therefore, we restricted ourselves to RCTs only. Considering the physiological differences between ELBW infants (< 1000 grams) and those between 1000–1500 grams, it may not be wise to club them under a single umbrella. Therefore, we attempted subgroup analysis for ELBW infants.

This systematic review suggests a three-hourly feeding schedule is as safe as two-hourly feeding in stable preterm infants with a birth weight between 1000 to 1500 grams. A three-hourly feeding schedule can be recommended in this subpopulation, considering the potential benefits of lower nursing workload, lesser handling of the neonate, and less mother-infant dyad stress. Most studies limited their follow-up till the infant achieved full tube feeds. So, there may be a concern whether three-hourly feeding with relatively larger volumes per feed would be suitable for transitioning from tube to oral feeding by spoon/cup. There is low-quality evidence that a three-hourly feeding schedule performs like two-hourly feeding in transitioning from tube to full oral feeds. This review also provides evidence that the same feeding schedule can be followed in SGA neonates.

Previous retrospective studies reported variable results with two feeding schedules [6, 7, 27]. For example, Chu et al. and Rudiger et al. compared 2-hourly vs. 3-hourly feeding schedules in ELBW infants and reported shorter (not statistically significant) time to reach full enteral in the 3-hourly feeding group [6, 7]. Also, the 3-hourly feeding group had a significantly shorter TPN duration and central catheter use but was associated with a more extended period of phototherapy and continuous positive airway pressure (CPAP) use. On the contrary, DeMauro et al. reported that infants fed at the two-hourly interval had better tolerance, achieved full enteral feeds earlier, and required less TPN [27]. However, all three studies reported a similar incidence of NEC with two feeding schedules. These variations might be due to differences in the feeding practices and are subject to potential limitations of retrospective studies.

This review of RCTs found that two-hourly feeding in ELBW infants helps to reach full enteral feeds by 2.9 days earlier (low certainty evidence). Our review also suggests that three-hourly feeding does not increase

the risk for feed intolerance, hypoglycemia, and apnea in this subpopulation but with very low certainty of the evidence. The authors did not report the incidence of NEC in this subpopulation. Thus, there is a definite need for further RCTs focused on ELBW infants. However, considering the benefits of 2-hourly feeding to achieve full enteral feeds earlier and no information about NEC, we suggest continuing 2-hourly feeding in ELBW neonates till further evidence.

Limitations

Although we followed standard guidelines for this review and used the GRADE framework to assess the certainty of the evidence, this review has few limitations. Most of the included trials were small and not adequately powered for critical outcomes like mortality and NEC. The number of ELBW neonates was too low to make robust conclusions. Also, due to lack of blinding, they were at high risk for performance and detection bias for many outcomes. All trials used mixed feeding but did not analyze the effect of the type of feeds; therefore, we cannot rule out the impact of formula milk on adverse outcomes like NEC or feed intolerance. There was wide variation in the volume and rate of advancement of feeds and the definition of full enteral feeds across the studies. Non-availability of data according to gestation, type of feed, and antenatal doppler abnormalities precluded specific sub-group analyses. Also, the trials did not study the effect of feeding intervals on maternal and infants stress levels, quality and duration of sleep, kangaroo mother care, anthropometry parameters at follow-up, and neurodevelopmental outcome.

Conclusions

Based on limited low to moderate certainty evidence, we suggest three hourly feedings in stable preterm infants with birth weight 1000 grams and more. However, for extremely low birth weight (< 1000 grams) infants, we suggest continuing two-hourly feeding until further evidence is available.

Abbreviations

- CI- Confidence Interval
- CVC- Central Venous Catheter
- ELBW- Extremely Low Birth Weight
- GRV- Gastric Residual Volume
- LBW- Low Birth Weight
- MD- Mean Difference
- NEC- Necrotizing Enterocolitis
- PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-analyses
- RCT- Randomized Controlled Trial
- RR- Risk Ratio
- RD- Risk Difference

- SMD- Standardized Mean Difference
- TPN- Total Parenteral Nutrition

Declarations

Funding: The authors did not receive any funding for this work.

Conflicts of interest: The authors declare no conflict of interest related to this work.

Availability of data and material: The data is given in the manuscript. The primary source of information is already available in the public domain.

Code Availability: Not applicable

Author Contribution

JK- Conceived idea, did literature search, retrieved, and analyzed the data, and drafted the manuscript.

JM and PD- Peer-reviewed search strategy, did literature search, analyzed the data, and drafted the manuscript.

PK- Conceived idea, supervised data synthesis and analysis, and critically reviewed the manuscript.

JS and AS: Provided critical inputs in data analysis and critically reviewed the manuscript.

All the authors approved the final version of the manuscript and shall be accountable for all aspects of the manuscript.

Ethics approval: Not required.

Consent to participate: Not required.

Consent for publication: All authors consented to publication.

Acknowledgment: A portion of this work was done to develop Clinical Practice Guidelines on 'Feeding of low-birth-weight neonates' for the National Neonatology Forum of India. We want to extend our sincere gratitude to all the guideline development group members for their valuable inputs.

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Figures

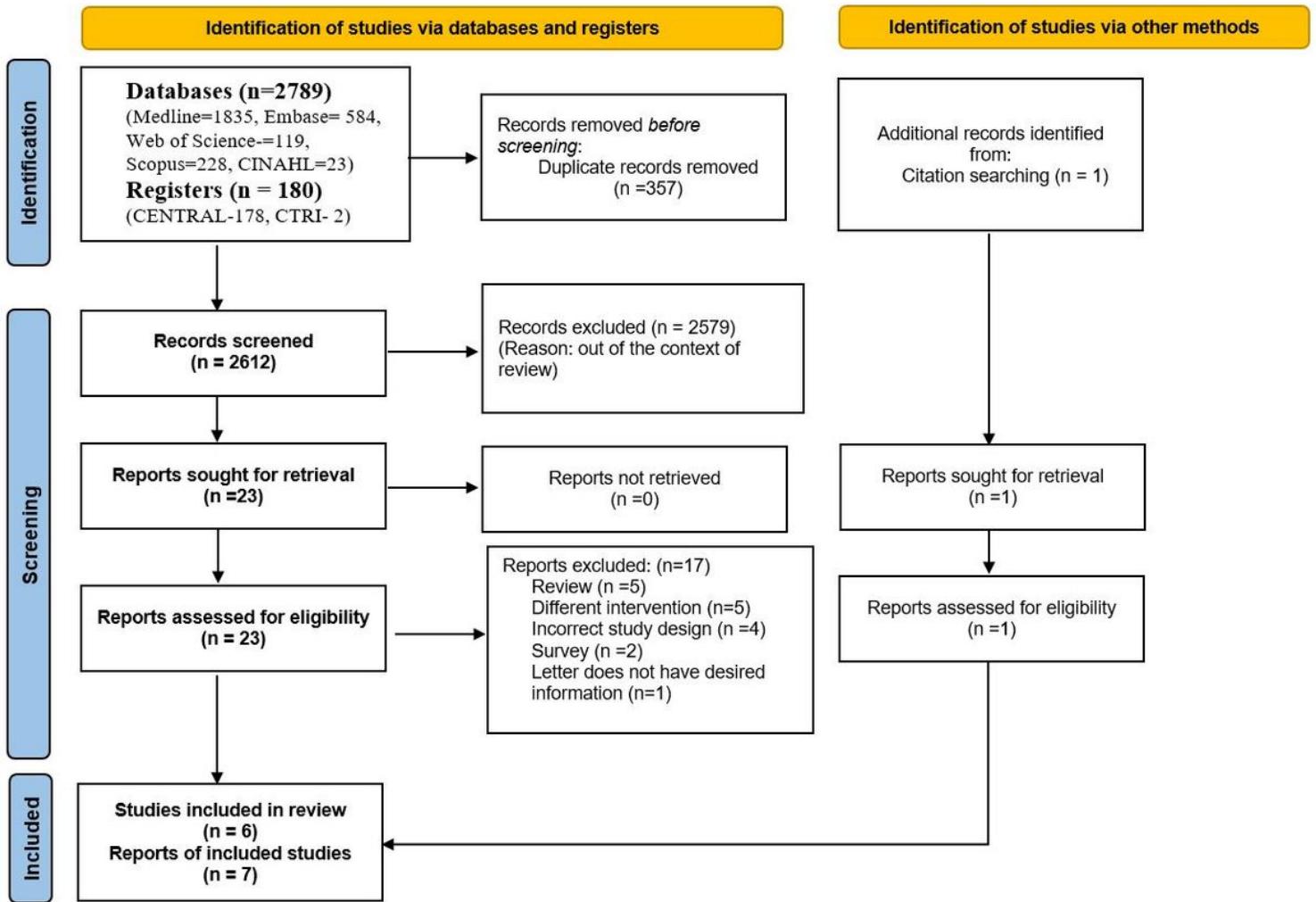


Figure 1

PRISMA Flow-Chart

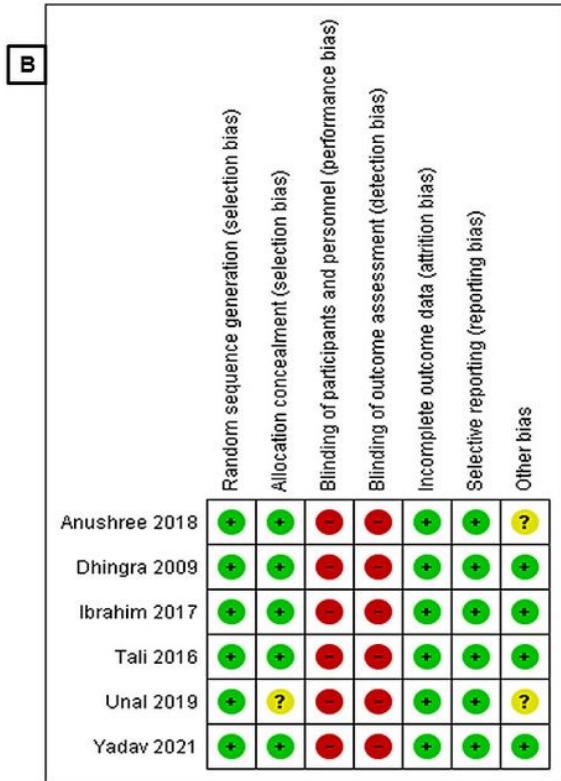
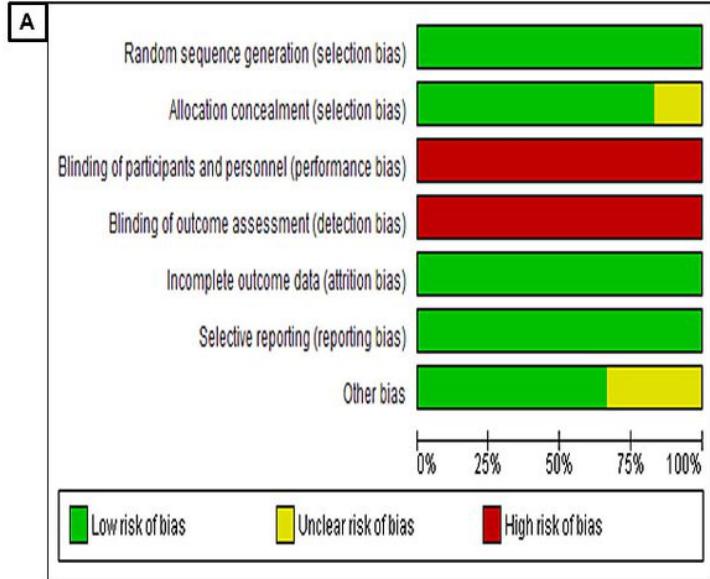


Figure 2

a) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies; b) Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

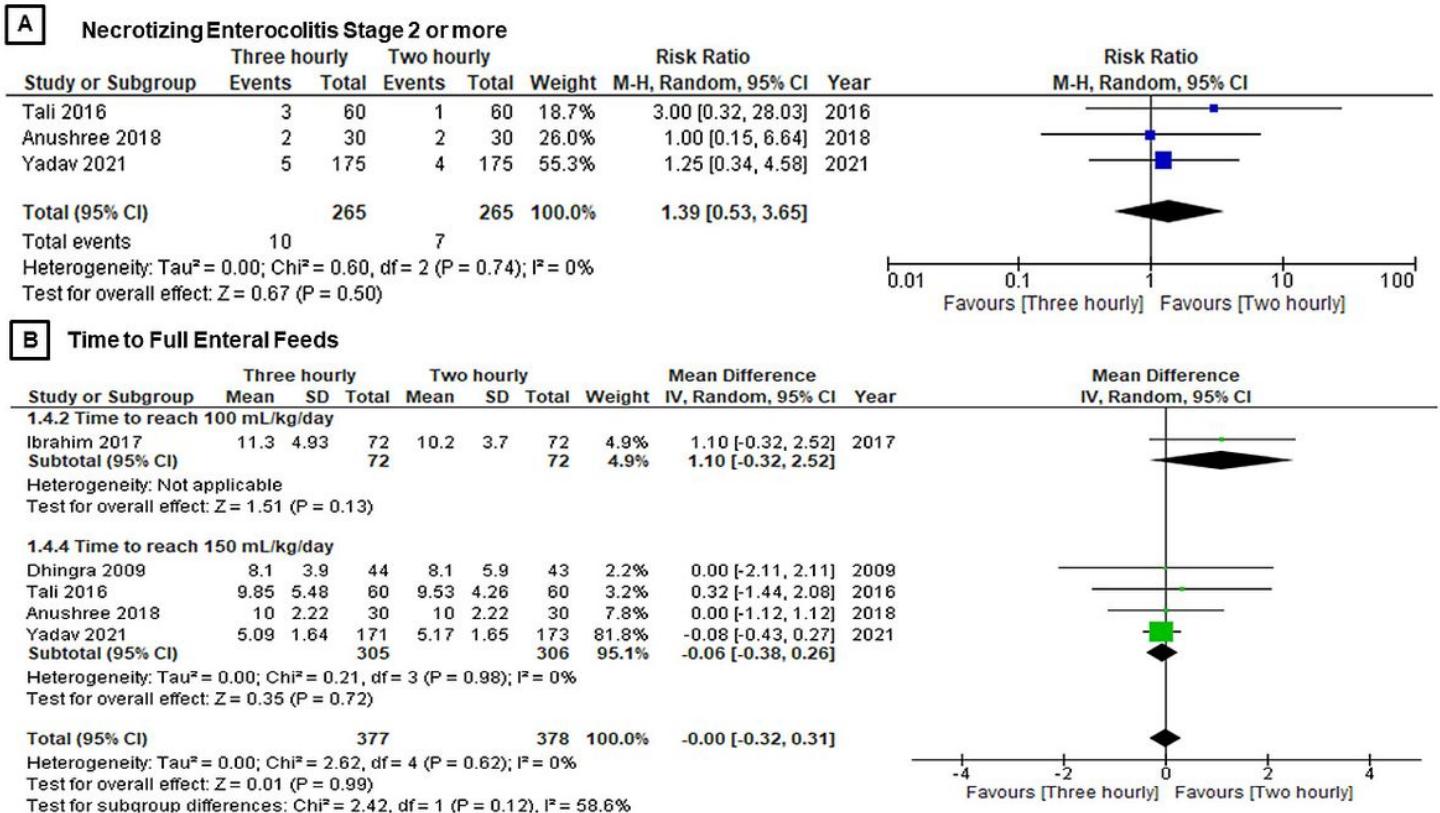


Figure 3

Forest-plot showing a comparison of Necrotizing enterocolitis stage 2 or more (3a) and time to reach full enteral feeds (3b) between three-hourly and two-hourly feeding schedules

Supplementary Files

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