Rapid versus Slow Feeding Advancement in Preterm Low Birth Weight Neonates: A Systematic Review and Meta-analysis

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ABSTRACT

Objectives. To compare the clinical outcomes of rapid versus slow enteral feeding advancement in preterm low birth weight neonates.

Methods. Searches for randomized controlled trials evaluating the effect of rapid versus slow rate of enteral feeding advancement on the clinical outcomes of preterm, low birth weight neonates were performed in different databases. Two authors screened the articles for inclusion and statistical analysis was done using Review Manager Version 5.3 (RevMan) software.

Results. Six trials with a total of 680 subjects comparing enteral feeding advancement protocols were identified. The number of days to reach full feeds in rapid enteral feeding was shorter by 2.79 days (95% CI 1.39, 4.19) and time to regain weight by 3.72 days (95% CI 2.86, 4.59) compared to slow enteral feeding. There was no significant difference in the incidence of feeding intolerance (OR 0.69, 95% CI 0.42, 1.11) and NEC (OR 0.88, 95% CI 0.45, 1.72) between the two groups.

Conclusions. Rapid enteral feeding protocols reduce the time to establish full enteral feeds and to regain birth weight in preterm low birth weight neonates. Rapid enteral feeding may facilitate early discharge and help reduce hospital costs for the care of these neonates.

Key Words: enteral feeding advancement, rapid feeding, slow feeding, preterm, low birth weight neonates

INTRODUCTION

The last few months of gestation are a critical period of growth and development of the fetal brain and body. Preterm neonates miss this opportunity, which makes them at risk for developmental delays and extrauterine growth restriction (EUGR).[1] In addition, these neonates also have poor oromotor tone, difficulty with sucking, and coordination of swallowing. High metabolic demands, decreased gut motility, and poor tolerance of enteral feeding may also affect their ability to absorb and utilize nutrients. This can lead to poor growth, which in turn is associated with poor outcomes in terms of growth and neurodevelopment at 18 to 24 months corrected age, in some studies, it is even noted to have an impact of 6 to 15 IQ points. Children who achieved greater in-hospital growth rate are less likely to have growth restriction at 18 months corrected age as well as lower risk of cerebral palsy, neurodevelopmental impairment (including blindness and deafness), Bayley and

Paper presented in the 35th Residents' Annual Research Week UP-PGH Department of Pediatrics on October 18, 2019 at the UP-PGH Science Hall.

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Psychomotor Development Index scores less than 70, and re-hospitalizations.[2] Quick weight gain has been attributed to early initiation of feedings, attaining full enteral feedings earlier, and receiving fewer days on parenteral nutrition.

The growth and maturation of the gastrointestinal tract rely highly on enteral nutrition. Studies show that inadequacy of enteric nutrition can predispose to gastrointestinal mucosa atrophy, decreased protective mucus, decreased lactase action, and increased gut permeability. These in turn could lead to dysfunction and a higher risk for feeding intolerance as well as necrotizing enterocolitis (NEC).[3] A Cochrane review reported that early initiation of minimal feeding produced a considerable decrease in time to reach full enteral feeds, duration of parenteral nutrition, and shorter duration of hospitalization.[4]

Necrotizing enterocolitis is the most encountered gastrointestinal emergency, especially in premature neonates. It is estimated to occur in one to three per 1000 live births with more than 90% occurring in very low birth weight infants born at less than 32 weeks of gestation. Its pathogenesis remains unknown but is most likely a multifactorial process that requires a concurrent host susceptibility (immunologic and intestinal immaturity), environmental triggers that lead to microbial dysbiosis, mucosal injury, and exaggerated inflammatory host response. It presents with feeding intolerance, nonspecific systemic signs (e.g., apnea, respiratory failure, poor feeding, lethargy, or temperature instability), and abdominal signs (e.g., abdominal distension, bilious gastric retention, and/or vomiting, tenderness, rectal bleeding, and diarrhea). The severity of NEC is defined by the severity of clinical findings, also called the Bell staging criteria (Figure 1).[5]

As mentioned earlier, premature infants have underdeveloped oromotor tone; hence, most need to be fed through an orogastric tube. Since the baby cannot control the amount of milk they receive, the caregiver must determine the amount of feeds. In very low birth weight neonates, the ideal speed at which feeds is delivered to these subsets of patients remains unclear. Increasing the amount of feeds little by little may lead to a lack of nutrition for the infant. On the other hand, several retrospective studies have suggested that rapid feedings (more than 25 ml/kg per day increments) may increase the risk of NEC. There are also studies comparing feedings at 15 to 20 ml/kg/day and 30 to 35 mg/kg/day and found out that the incidence of NEC did not differ between the two groups.[6,7]

Providing optimal nutrition for the premature infant is a crucial task for pediatricians since this has a significant influence on the future maturation and neurodevelopment of these patients. Full and continuous enteral nutrition in babies with low birth weight is particularly difficult considering the intrinsic issues of immature intestinal motility and function, as well as the fear of NEC when feeding is progressed too rapidly. This review is directed at resolving the effects of fast versus slow enteral feeding advancement on time to achieve complete feeds, the incidence of NEC, and other clinical outcomes.

METHODS

Inclusion criteria

a. Type of studies

Randomized controlled trials (RCT) evaluating the effect of rapid versus slow rate of enteral feeding advancement on the clinical outcomes of preterm, low birth weight neonates

b. Type of participants

Enterally fed stable preterm (<35 weeks) and low birth weight (<2000) neonates hospitalized at the NICU of the different hospitals where the study took place

Stage	Classification of NEC	Systemic signs	Abdominal signs	Radiographic signs
IA	Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric retention, abdominal distention, emesis, heme-positive stool	Normal or mild intestinal dilation, mild ileus
IB	Suspected	Same as above	Grossly bloody stool	Same as above
IIA	Definite, mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis
IIB	Definite, moderately ill	Same as above, plus mild metabolic acidosis and thrombocytopenia	Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIA, plus ascites
IIIA	Advanced, severely ill, intact bowel	Same as IIB, plus hypotension, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention	Same as IIA, plus ascites
IIIB	Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	Same as above, plus pneumoperitoneum

Figure 1. Modified Bell staging criteria for NEC.[5]

c. Type of intervention

Different rates of progression in the advancement of feedings ranging from daily increments of up to 20 ml/kg for the slow group and up to 35 ml/kg for the rapid group with feedings started at the same post-conceptional age in each group.

d. Type of outcome measures

i. Primary outcome
Number of days taken to achieve full enteral feeds

ii. Secondary outcomes
Time to regain weight, incidence of feeding intolerance and NEC.

Search strategy

Electronic searches

We searched CENTRAL, MEDLINE (through PubMed), Google Scholar, Clinical Trials Registry , Scopus, LILACS, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) until September 2019. We also searched secondary sources such as conference proceedings, and reference lists of previous reviews and retrieved articles. We used the keywords "rapid versus slow enteral feeding", "fast versus slow feeding advancement", "preterm low birth weight neonates" and "randomized controlled trial" along with similar MeSH terms, appropriate Boolean operators, and without language restrictions. Related citations of the articles that were retrieved were also searched to obtain other possible studies.

Data Collection and Analysis

Study Selection

Two reviewers screened all titles and abstracts from the search. Full-text articles of potentially relevant RCTs were retrieved and only those with fulfilled inclusion criteria were included. Two review authors independently appraised each article. In case of discrepancy, a third author was consulted.

Data Extraction

The authors extracted data independently from the included studies. Data was then checked for errors and entered into the Review Manager Version 5.3 (RevMan) software.

Risk of Bias Assessment

The review authors individually evaluated the risk of bias (low, high, or unclear) of all included trials using the Cochrane Risk of bias tool using the following domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting.[8]

Measures of Treatment Effect

Effect of treatment was measured using mean difference (MD) for continuous data and odds ratio (OR) for dichotomous outcomes, with respective 95% confidence intervals (CIs).

Unit of Analysis Issues

The unit of analysis was the participating neonate in individually randomized trials.

Assessment of Heterogeneity

We assessed heterogeneity between trials by inspecting forest plots and calculating the I^2 statistic for each analysis.

Data Synthesis

Review Manager Version 5.3 (RevMan) software was utilized for statistical analysis. We used the random-effects model because heterogeneity in the sampled population was likely, which was due to the varying capability and health infrastructures in the different centers of the different countries. Reanalysis was done by analyzing the data using a fixed effect model and by changing measures for dichotomous outcomes (Supplementary Figure 1).

RESULTS

Results of the Search

An extensive search was made through several databases including PubMed, Google Scholar, Scopus, Lilac, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Herdin, and Cochrane Library. The literature search yielded 213 records. We excluded 200 titles and abstracts that did not fulfill the inclusion criteria. Thirteen complete articles were retrieved and evaluated. Seven articles were excluded based on the following reasons: two articles lacked the outcomes in question, another two articles had unclear exclusion criteria which may lead to possible selection bias, two articles were systematic review articles, and one article was an ongoing trial. Ultimately, the final review included six studies (Figure 2).

Study Characteristics

Six papers met the review eligibility criteria with a total of 680 subjects. All studies were randomized controlled trials conducted in neonatal intensive care units in North America, India, Turkey, and Bangladesh. Participants weighed between 500 - 2000 g with a gestational age of < 35 weeks. All studies started enteral feeding within the first seven days after birth with variable rates of feeding advancement in each study. In the study by Rayyis and colleagues, only babies fed with milk formula were eligible for participation, while in the remainder of the studies participating neonates have been supplied with expressed breast milk. Most of the trials had identified criteria for disrupting milk feedings, such as more than 30% of the previous meal gastric residuals, distended

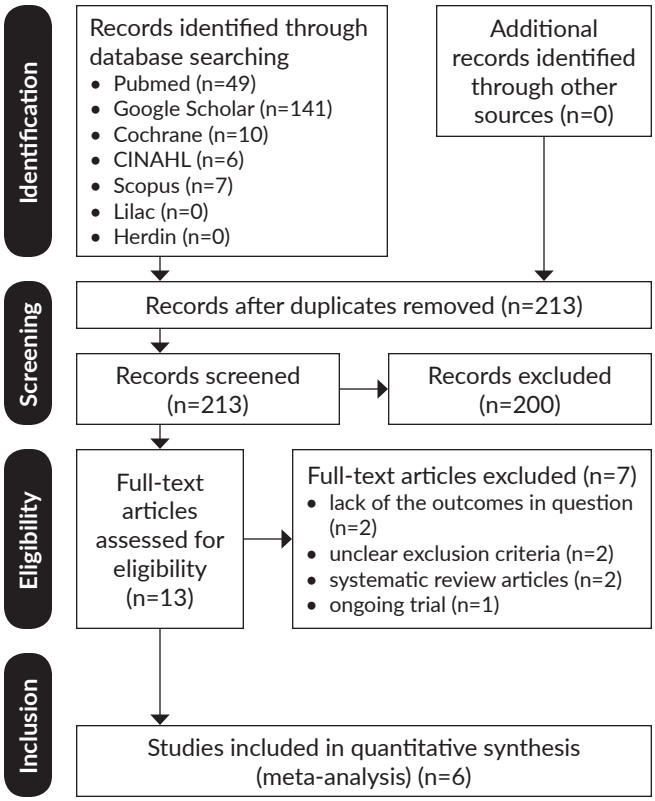

Figure 2. PRISMA flow diagram.

abdomen, persistent vomiting, or detection of fecal occult blood. The outcomes reported in the studies included duration to establishing complete enteral feeding, time to recover birth weight, length of hospitalization, frequency of NEC, and rates of invasive infection. Table 1 shows the summary of the characteristics of the studies included in the review.

In the trial by Rayyis et al., which was conducted from January 24, 1994, to December 30, 1996, in a NICU at the University of Alabama at Birmingham, 187 neonates with a birth weight of 501 to 1500 g and < 34 weeks age of gestation were enrolled. The participants were randomly assigned to receive 15 ml/kg/day (i.e., slow group) and 35 m/kg/day (i.e., fast group) increments of enteral feedings of milk formula. Results from this study showed that the fast group reached full enteral feeds earlier (11 days versus 15 days, P < 0.001) and reached their birth weight faster (43 days versus 47 days, P = 0.3) compared to the slow group. The incidence of NEC (13% and 9% for slow and fast respectively, P = 0.5) and age at discharge (47 and 43 days for slow and fast group, respectively, P = 0.3), however, were not statistically significant between groups.[9]

Salhotra and colleagues conducted a study on 53 preterm, very low birth weight neonates in a NICU in India. The neonates were randomized into the slow advancement group (15 ml/kg daily increment of feeding) or fast advancement group (30 ml/kg daily increment of feeding advancement). It was noted that the fast advancement group completed

Table 1. Summary of Characteristics of Studies Included in the Review

Study and Country	Design	Setting/Study Population	Intervention	Outcomes of Interest
Rayyis et al. (1999) [9] ***USA***	Prospective randomized controlled trial	NICU, n=185 infants weighing 501 to 1500 g, ≤ 34 weeks gestational age	Enteral feeding advancement at daily increments of 15 ml/kg and 35 ml/kg	Incidence of Necrotizing enterocolitis, Days to reach full feeds, Days to regain birth weight, Postnatal age at discharge
Salhotra et al. (2003) [10] ***India***	Randomized controlled trial	NICU, n=53 stable neonates weighing < 1250 g with gestational age ≤ 35 weeks	Daily enteral feeding advancement of 15 ml/kg and 30 ml/kg	Days to reach full enteral feeds (defined as 180 ml/kg/day), Number of cases of necrotizing enterocolitis, apnea and feeding intolerance
Caple et al. (2004) [11] ***USA***	Prospective randomized controlled trial	NICU, n=155 neonates weighing 1000 - 2000 g with gestational age ≤ 35 weeks	Enteral feeding advancement with daily increments of 20 ml/kg and 30 ml/kg	Days to complete feedings, Days to regain birth weight, Duration of intravenous fluids, Duration of hospitalization, Number of cases of feeding intolerance and necrotizing enterocolitis
Krishnamurthy et al. (2009) [12] ***India***	Prospective randomized controlled trial	NICU, n=100 neonates with birth weight of 1000 - 1499 g, < 34 weeks age of gestation	Enteral feeding advancement of 20 ml/kg per day or 30 ml/kg per day	Days to complete feedings, Frequency of necrotizing enterocolitis, apnea and feeding intolerance, Days on parenteral nutrition, Length of hospital stay, Time to regain birth weight
Karagol et al. (2012) [13] ***Turkey***	Prospective randomized controlled trial	NICU, n=92 neonates weighing 750 – 1250 g and ≤ 32 weeks of gestation	Daily enteral feeding advancement of 20 ml/kg or 30 ml/kg	Time to reach complete enteral feeding (defined as 180 mL/kg/day), Incidence of feeding intolerance, necrotizing enterocolitis and sepsis, Duration of parenteral nutrition and of hospitalization, Time to regain birth weight
Ahmed et al. (2017) [14] ***Bangladesh***	Prospective randomized controlled trial	NICU, n=95 infants weighing <1500 g with gestational age ≤ 35 weeks. Stratification done according to weight, < 1250 g and < 1500 g.	For 1000 - 1250 g, advancement was done in done in daily increments of 10 ml/kg and 15 ml/kg. For 1251 - 1500 g, advancement was done in 15 ml/kg per day and 20 ml/kg per day increments.	Time taken to achieve full enteral feeds, Episodes of feeding intolerance, necrotizing enterocolitis and apnea, Days on parenteral nutrition, Duration of hospitalization, Time to regain birth weight

enteral feed earlier (10 ± 1.8 days versus 14.8 ± 1.5 days, P < 0.001) and regained birth weight quicker (11.9 ± 4 days versus 12.5 ± 4.1 days, P < 0.001) compared to the slow advancement group. There was no difference between groups in terms of incidence of feeding intolerance (14 patients for the fast group and 17 for the slow group, respectively), apnea (9 for both groups), and NEC (only two neonates, both from the fast group).[10]

In the study by Caple et al., 155 neonates weighing 1000 and 2000 g and ≤ 35 weeks in gestational age admitted in a NICU in Houston, Texas were randomized to receive feeding advancements at either 20 ml/kg/day (control group) or 30 ml/kg/day (intervention group). Results showed that babies in the intervention group achieved complete enteral feeds earlier (7 versus 10 days for intervention and control group respectively, P < 0.01), regained their birth weight earlier (11 and 13 days for intervention and control group respectively, P < 0.01), and had shorter time on parenteral nutrition (6 versus 8 days for intervention and control group respectively, P < 0.01). The incidence of NEC did not vary significantly between interventions (two and three neonates in the control and intervention group respectively, P = 0.66).[11]

Krishnamurthy and associates performed their study on 100 newborns weighing 1000 and 1499 g with gestational age less than 34 weeks in a NICU in India between February and September 2008. Participants were randomly allocated into the slow advancement group (defined as 20 ml/kg daily) and the rapid advancement group (defined as 30 ml/kg daily). Neonates in the rapid feeding group achieved complete enteral feedings sooner (average 7 vs. 9 days, P < 0.001), recovered birth weight earlier (average 16 versus 22 days, P < 0.001), had fewer days on parenteral nutrition (average 2 versus 3.4 days, P < 0.001), and had a shorter length of hospital stay (average 9.5 versus 11 days, P = 0.003). The incidence of apnea (14 in slow group versus 9 in the rapid group, P = 0.24), feeding intolerance (5 versus 4 in slow and rapid group respectively, P = 0.73), NEC (1 in slow group versus 2 in the rapid group, P = 1.0), or overall mortality (6 versus 4 in slow group and rapid group correspondingly, P = 0.51) were not significantly different between groups.[12]

Karagol et al. reported that between January 2010 and February 2011, 92 preterm neonates (< 32 weeks of age) weighing 750 - 1250 g were admitted at the NICU of Dr. Sami Ulus Maternity, Children's Education and Research Hospital in Turkey. Eligible participants were stratified by birth weight (i.e., 750 - 1000 g and 1000 - 1250 g birth weight) and randomly divided into two groups: slow and rapid advancement group. Feeding was provided at daily increments of 20 ml/kg in the slow advancement group while feeding was advanced at 30 ml/kg in the rapid advancement group until full feeds of 180 ml/kg/day was reached. Participants in the rapid enhancement group for both weight strata achieved full feeds faster (750 - 1000 g: 24.1 ± 11.8 versus 26.7 ± 15.2 days, P = 0.02; 1001 - 1250 g: 19.1 ± 4.3 versus 22.3 ± 6.4 days, P = 0.001), spent lesser time on parenteral nutrition (750 - 1000 g: 21.6 ± 16.3 versus 23.0 ± 18.6 days, P = 0.01; 1001-1250 g: 17.6 ± 9.2 days, P = 0.001; 1001 - 1500 g: 19.2 versus 23.0 days, P = 0.005), shorter duration of hospitalization (750 - 1000 g: 34.4 versus 40.7 days, P = 0.002; 1001 - 1500 g: 29.2 versus 35.1 days, P = 0.001) and incidence of culture proven sepsis (750 - 1000 g: 3 versus 4, P = 0.84; 1001 - 1500 g: 3 versus 6, P = 0.02) compared to their counterparts in the slow advancement group. The incidence of NEC (750 - 1000 g: 2 versus 1, P = 0.21; 1001 - 1500 g: 2 versus 4, P = 0.53) and feeding intolerance (750 - 1000 g: 6 versus 8, P = 0.76; 1001 - 1500 g: 5 versus 5, P = 0.38) were not statistically different between groups.[13]

In the study by Ahmed et al., between April 2013 and July 2014, 95 neonates from Bangabandhu Mujib Medical University NICU were stratified into two birth weight groups (1000 to < 1250 g and 1250 g to < 1500 g) and then randomly allocated into two groups. Feeding was advanced at 10 ml/kg per day and 15 ml/kg per day in slow and rapid advancement groups for 1000 to < 1250 g infants, accordingly. In infants weighing 1250 to < 1500 g, feeding was advanced in increments of 15 ml/kg per day and 20 ml/kg per day in the slow and rapid advancement groups, respectively. In both birth weight strata, the rapid group completed enteral feeds faster (< 1250 g: 21.9 ± 3.5 versus 18.1 ± 3.1 days, P = 0.001; > 1250 g: 16.2 ± 3 versus 13.4 ± 3.6 days, P = 0.009). In addition, the rapid advancement group also had a shorter duration of parenteral nutrition (< 1250 g: 19.9 ± 3.3 versus 16.3 ± 3.1 days, P = 0.002; > 1250 g: 14.4 ± 3.1 versus 11.6 ± 3.6 days, P = 0.01) and earlier regaining of weight (< 1250 g: 21.5 ± 4.5 versus 18 ± 2.9 days, P = 0.01; > 1250 g: 16.4 ± 3.3 versus 13.5 ± 3.5 days, P = 0.02). The number of feeding intolerance, apnea, sepsis, NEC, and duration of hospitalization were not statistically different between the slow and rapid advancement groups.[14]

Risk of bias in included trials

Figure 3 shows a graphical summary of the risk of bias of the included studies.

Randomization and Allocation (Selection Bias)

Studies by Karagol et al., Krishnamurthy et al., and Salhotra et al. all used a computer-generated series of randomization to distribute the subjects, and allocation was hidden using sealed, opaque envelopes. On the other hand, Rayyis et al. and Caple et al. used blinded, random draw, numerical assignment for randomization; however, they did not mention how allocation was carried out. Randomization and allocation were not clearly stated in the study by Ahmed et al.

Blinding (Performance and Detection Bias)

The feeding strategies to which participants were assigned were not concealed from the parents, caregivers, or clinical investigators in all the included trials. This task

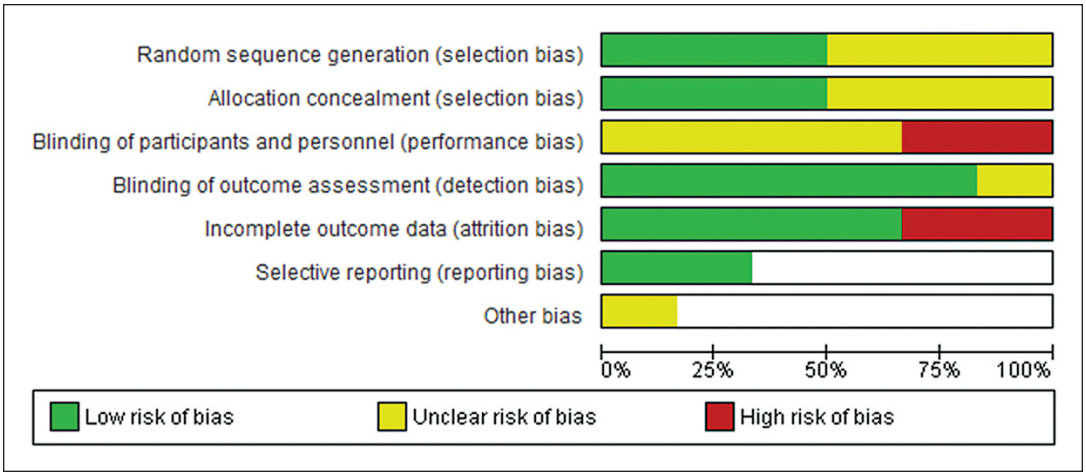

Figure 3. Risk of bias graph.

is difficult, if not impossible, due to the characteristics of the interventions and for patient safety as well.

Incomplete Outcome Data (Attrition Bias)

In the study by Ahmed et al., two infants did not finish the study; however, the reason for the dropouts was not mentioned. Data of these patients were excluded from the analysis. In the study by Rayyis et al., there were seven dropouts due to the following reasons: transfer to a different hospital before receiving full feeds, the patient was withdrawn from the study as requested by the attending physician due to multiple episodes of feeding intolerance, and parent's request to feed the baby with human milk. Data from these infants were still evaluated because the analysis was done based on intention to treat. In the study by Salhotra et al., 19 participants died (7 from the fast group and 12 from the slow group) but their data were still included in the final analysis. The causes of death of the aforementioned were sepsis, NEC, respiratory distress syndrome, prematurity, inborn error of metabolism, and pulmonary hemorrhage.

Selective Reporting (Reporting Bias)

The results of all previously identified outcomes were reported in each of the six studies. Funnel plots were not utilized to assess reporting bias since there were less than 10 studies included in the review.

Effects of intervention

Primary Outcome

Meta-analysis of data from the six studies showed that the mean number of days to reach full feeds in rapid enteral feeding was shorter by 3 days (2.79 days, 95% CI 1.39, 4.19; $p < 0.001$, $I^2 = 82\%$) compared to slow enteral feeding (Figure 4). One trial listed the data separately for infants weighing 1000 - 1250 g and those weighing 1250 - 1500 g. Among the studies analyzed, one study (Caple et al.) was an outlier and showed a higher but statistically insignificant increase in feeding time for the rapid feeding group. The estimated value was computed based on the median and range values provided by the study.

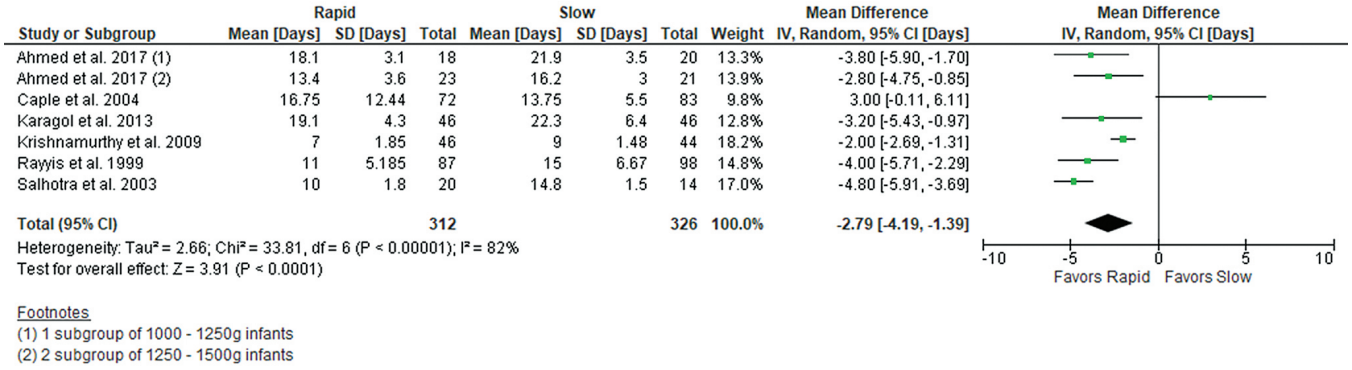

Figure 4. Forest plot comparing time to reach full enteral feeds for rapid and slow feeding advancement.

**Forest plot showing the number of days to reach full enteral feeds in rapid group was shorter by 2.79 days (95% CI 1.39 – 4.19, p < 0.001) compared to slow group.*

Secondary Outcomes

The six trials showed that the time to regain weight was shorter with rapid enteral feeding by almost 4 days (3.72 days, 95% CI 2.86, 4.59; p < 0.001, I^2 = 0%) compared to slow enteral feeding (Figure 5). Four studies showed that there was no significant difference in the incidence of feeding intolerance between rapid and slow enteral feeding (pooled OR 0.69, 95% CI 0.42, 1.11; p = 0.13, I^2 = 0%) (Figure 6). Moreover, five studies showed no significant difference between rapid and slow enteral feeding groups in the incidence of NEC (pooled OR 0.88, 95% CI 0.45, 1.72; p = 0.56, I^2 = 0%) (Figure 7).

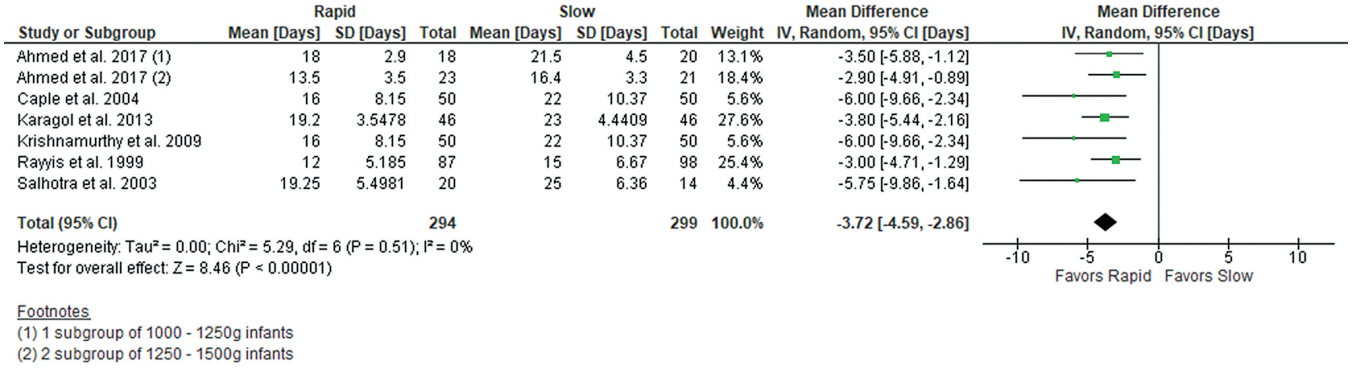

Figure 5. Forest plot comparing time to regain birth weight for rapid and slow feeding advancement.

**Analysis of the six studies showed that time to regain weight is shorter in the rapid group by 3.72 days (95% CI 2.86 – 4.59, p < 0.001) compared to the slow feeding group with low heterogeneity (I^2=0%).*

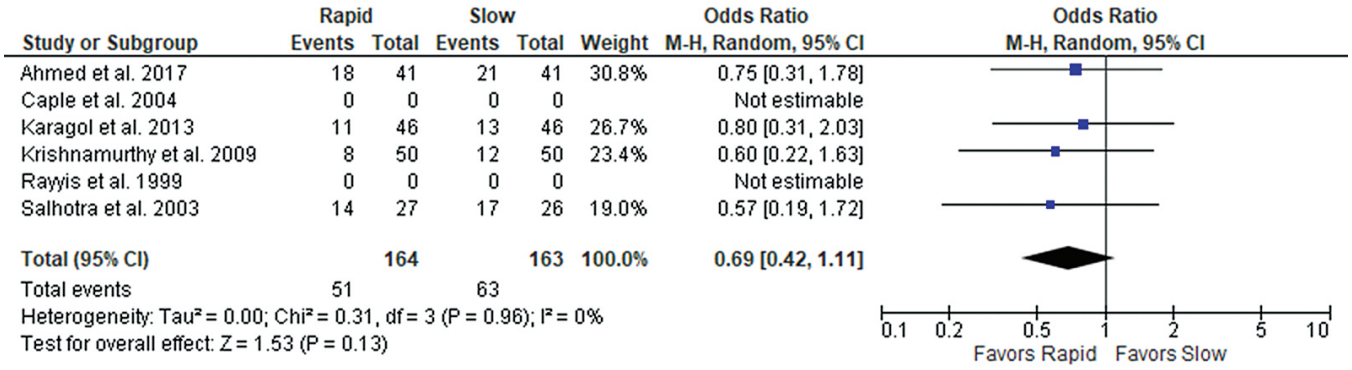

Figure 6. Forest plot comparing incidence of feeding intolerance for rapid and slow feeding advancement.

**There was no significant difference in the incidence of feeding intolerance between rapid and slow enteral feeding group (pooled OR 0.69, 95% CI 0.42 – 1.11, p = 0.13, I^2=0%).*

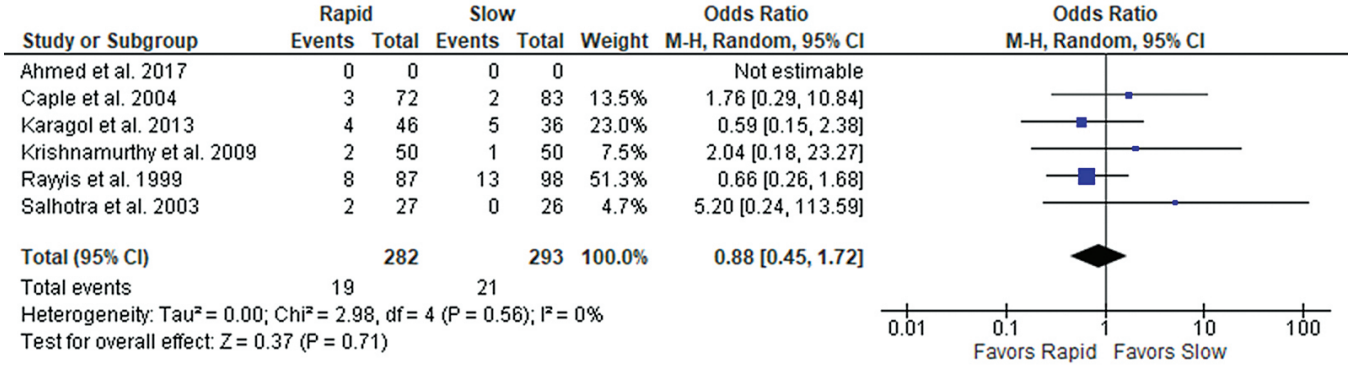

Figure 7. Forest plot comparing incidence of necrotizing enterocolitis for rapid and slow feeding advancement.

**There was no significant difference in the incidence of feeding intolerance between rapid and slow enteral feeding group (pooled OR 0.88, 95% CI 0.45 – 1.72, p = 0.56, I^2=0%).*

DISCUSSION

Timely and appropriate enteral nutrition is essential for survival in preterm and especially low birth weight neonates. However, many preterm low birth weight neonates have delayed establishment of enteral feeding due to apprehension of NEC or feeding intolerance. This causes utilization of intravenous fluid or total parenteral nutrition, which, in turn, puts the neonate at risk for increased rates of bloodstream infection or sepsis. In resource-limited neonatal intensive care units, it is more likely to have poor asepsis protocols and overcrowding.[15] Furthermore, late-onset infection and NEC are associated with reduced nutrient intake and a higher incidence of long-term neurological disability.[16] On the other hand, the establishment of early enteral feeding helps healthy gut microbes to grow and assists in the maturation of the gut, which in turn lessens the risk for NEC.[17]

In the studies included in this review, feeding intolerance was defined as gastric residuals of more than 50% of the prefeed volume, vomiting of more than three times in a 24-hour period, bile or blood-stained vomitus or residuals, abdominal distention, abdominal wall tenderness or erythema, and gross/occult blood in stools. Feeding intolerance is a requirement to cease enteral feeding temporarily and to work up for NEC and sepsis. Pediatric radiologists without knowledge of group assignment interpreted all abdominal radiographs. Diagnosis of NEC was made based on clinical and radiological features according to Bell's criteria. The study endpoint was the development of NEC IIA or greater.

This review aimed to compare the effectiveness of rapid enteral feeding advancement in decreasing duration to complete enteral feeds and regaining birth weight as well as the incidence of feeding intolerance and NEC. Pooled mean data from the six trials showed a statistically significant effect of rapid enteral feeding advancement on decreasing time to complete enteral feeds as well as time to recover birth weight. However, it should be noted that the studies were highly heterogenous with respect to this outcome (I^2 = 82%). One of the studies show a higher but statistically insignificant increase in feeding time. The results of the study by Caple et al. were median and range values and had to be converted to mean and standard deviation values. The study had a wide range of values which could have led to the study being an outlier.

The trial data in this review also provided evidence that rapid enteral feeding progression had no statistically significant effect on the risk of feeding intolerance and NEC in preterm low birth weight neonates. Most of the participants were preterm low birth weight neonates appropriate for gestational age thus making the review findings relevant to populations at most risk of acquiring feeding intolerance or NEC. The trial by Rayyis et al. restricted participation to exclusively formula-fed infants while in the rest of the trials the participants are only partially fed with formula milk. There is indeed evidence that the prevalence of NEC and feeding intolerance is higher in formula-fed infants.[18] In this study, however, this factor does not affect the outcome measured, i.e., the odds ratio of NEC for slow versus rapid feeding advancement. Figure 6 clearly shows that the point estimate and confidence intervals for the Rayyis study largely overlap with those of the other included studies. The pathogenesis of NEC remains poorly understood. Early studies focused on the substance of feeding as one of the possible causes of NEC. This knowledge creates confusion as to the optimal rate or time of initiation of enteral feeding in neonates. Finding the best method to feed premature infants while minimizing complications is of paramount importance. The present review aims to offer some form of illumination to this issue.

The clinical importance of the finding that rapid feeding advancement speeds up the time to reach full feeds and time to regain birth weight seems intuitive; however, future studies on longer-term growth or developmental outcomes could be of great value. In addition, since extremely preterm or extremely low birth weight infants comprise only a small percentage of the total participants in the existing trials, the generalisability of these data for this subset of patients is unclear. It is also uncertain whether the review findings apply to infants who receive continuous intragastric feed infusions since the majority of the infants in the included trials received feeds as boluses. Further randomized controlled trials could provide more precise estimates of the outcomes under discussion for this subgroup of patients.

CONCLUSION

The review showed that advancing enteral feed volumes at rapid rates, typically up to 35 ml/kg, in preterm low birth weight neonates shortened by several days the time needed to establish full feeding as well as the time to regain birth weight. In addition, slow feeding rates, that is up to 20 ml/kg, did not show a difference in the risk of NEC and feeding intolerance. Results of this analysis may not apply to those who are moderately sick and with hemodynamic instability. In developing countries, rapid enteral feeding protocols can significantly decrease hospital morbidity and improve weight gain, which in turn results in shortened duration of hospital stay and consequently, reduced hospital costs for the care of these neonates.

Statement of Authorship

This study was reviewed principally by the primary author (ICG). Data were extracted and analyzed by ICG and JAG. Methodological quality was assessed by SAG, KAS, and FDO. All authors approved the final version submitted.

Author Disclosure

All authors declared no conflicts of interest and have no affiliation with any pharmaceutical or formula milk companies.

Funding Source

The study was personally funded.

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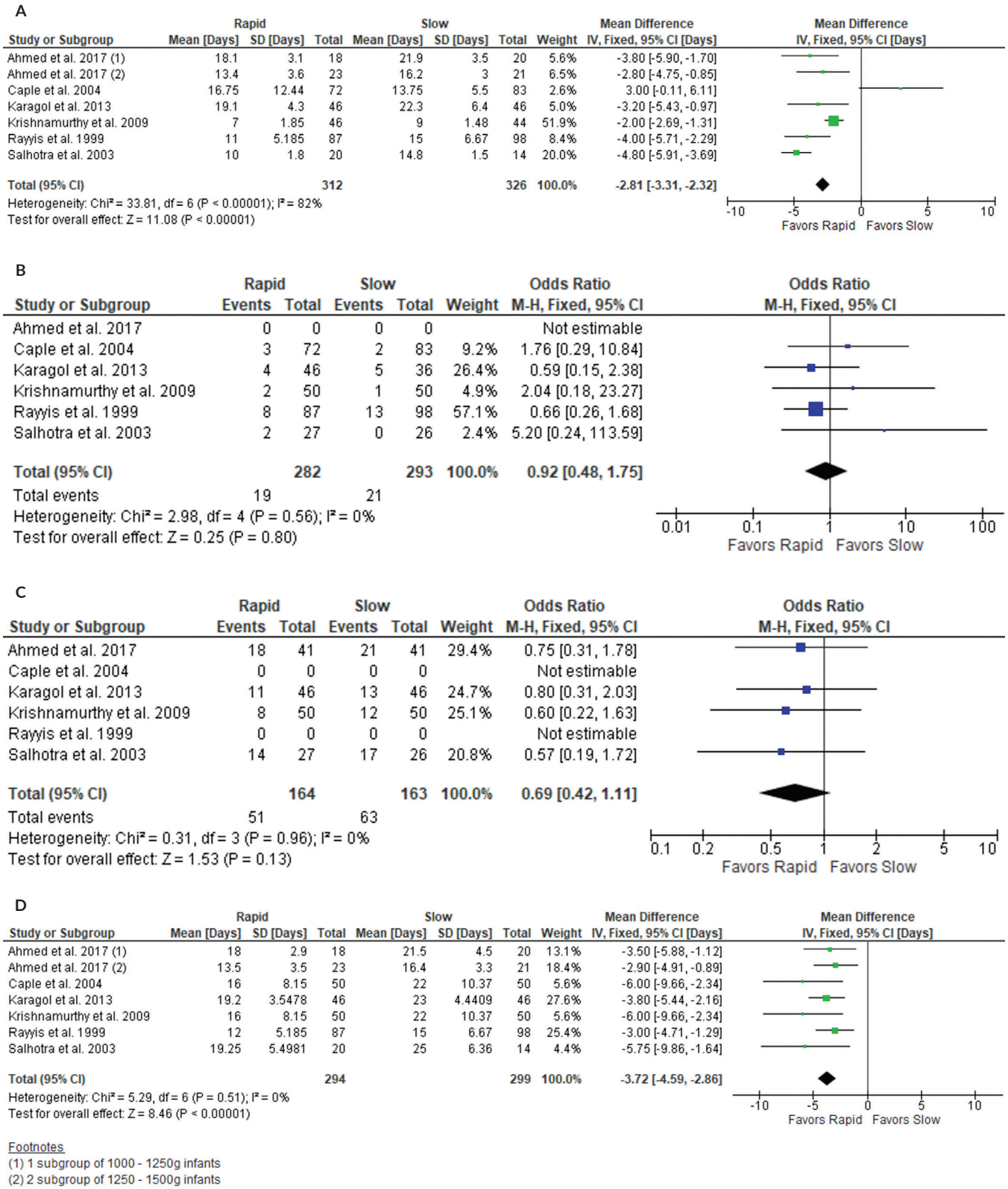
SUPPLEMENT



Supplementary Figure 1. Analysis of study outcomes using fixed-effects model. **(A)** Rapid vs Slow Enteral Feeding. **(B)** Incidence of Necrotizing Enterocolitis. **(C)** Feeding Intolerance. **(D)** Time to regain weight (Days).