

Enteral feeding strategies in preterm neonates \leq 32 weeks gestational age: A Systematic review and network meta-analysis

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Short title: Feeding in preterm neonates: Network meta-analysis

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Number of Tables – 2

Number of Figures – 3

Word count – Abstract - 249, Manuscript - 2661

Key words – Nutrition, NEC, VLBW, very preterm

ABSTRACT

Introduction: Critical aspects of time of feed initiation, advancement and volume of feed increment in preterm neonates remain largely unanswered.

Methods: MEDLINE, CENTRAL, EMBASE and CINAHL were searched from inception till until 25th September 2020. Network meta-analysis with Bayesian approach was used. Randomized controlled trials including preterm neonates ≤ 32 weeks were included. Feeding regimens were divided based on - *Initiation day*: early (< 72 hours), moderately early (72 hours - 7 days), late (> 7 days); *Advancement day*: early (< 72 hours), moderately early (72 hours - 7 days), late (> 7 days); *Increment volume*: small volume (< 20 ml/kg/day), moderate volume (20 - < 30 ml/kg/day), large volume (30 ml/kg/day) and full enteral feeding from first day. Sixteen regimens were evaluated. Combined outcome of necrotizing enterocolitis (NEC) stage \geq II or mortality before discharge was the primary outcome.

Results: 39 studies, 6982 neonates included. Early initiation with moderately early or late advancement using moderate volume increment enteral feeding regimens appeared to be most efficacious in decreasing the risk of NEC or mortality when compared to early initiation and early advancement with small volume increment [RR (95% CrI) - 0.39 (0.12, 0.95); 0.34 (0.10, 0.86)] (GRADE - Very low).

Conclusions: Early initiated, moderately early or late advanced with moderate volume increment feeding regimens might be most appropriate in decreasing the risk of NEC stage \geq II or mortality. In view of the certainty of evidence being very low, adequately powered RCTs evaluating these two strategies are warranted.

Introduction

Despite the major advances in neonatal care, there is paucity of consensus on the most appropriate enteral feeding strategy in very and extremely preterm neonates.[1] Enteral feeding is a modifiable factor for necrotising enterocolitis (NEC) and late onset neonatal sepsis (LOS), two important causes of morbidity and mortality in preterm neonates.[2,3] Whilst the fear of NEC can preclude physicians from initiating and advancing enteral feeds early in postnatal life, the possibility of acquiring LOS might encourage some to do so.

Broadly put, more than three decades of rigorous research on preterm enteral feeding has galvanized the shift of practice from enteral fasting to earlier initiation as well as advancement of enteral feeds in preterm neonates.[4-6] However, the safest window for initiation and advancement of feeds along with the rates of feed increment is still debated. Establishing successful enteral feeding and preventing NEC in preterm neonates is influenced by a multitude of biological as well as potentially modifiable factors, including receipt of antenatal corticosteroids, gestational age, intrauterine growth restriction as well as antenatal umbilical artery doppler flow status, the sickness profile, type of milk used, use of probiotics and broad spectrum antibiotics.[7,8] Due to such significant heterogeneity in the demographic characteristics of preterm neonates, alongside the interwoven practices determining the risk of NEC, there can be no single ‘silver bullet’ feeding regimen tailored to all.

Multiple systematic reviews (SRs) have evaluated the different aspects of preterm feeding in pair-wise meta-analyses.[4–6,9] Enteral feeding is a multifaceted intervention with many aspects such as time of initiation / advancement of feeds, volume of advancement, mode of feeding (bolus vs. continuous) etc. We hypothesize that evaluating the different enteral feeding strategies in a network meta-analysis (NMA) might be the most appropriate way to study their relative effectiveness. Henceforth, in this paper we systematically review the evidence related

to preterm enteral feeding and analyse the comparative effectiveness of the various regimens in a network meta-analysis.

Methods

This SR was registered with PROSPERO (CRD42020210760).[10] The reporting of this review is in accordance with the PRISMA – NMA extension.[11]

Literature Search

Electronic databases – MEDLINE, CENTRAL, EMBASE and CINAHL searched from inception until 25th September 2020 and no time limits were applied. (eTable-1) There were no language barriers. Two authors searched the titles and abstracts in duplicate. Full texts of relevant studies were extracted and evaluated for inclusion. Rayyan – QCRI software was used for the literature search.[12]

Inclusion criteria

Randomized controlled trials (RCTs) evaluating enteral feeding strategies in neonates of ≤ 32 weeks' gestational age were included. Studies that had enrolled small for gestational age (SGA) neonates with or without evidence of placental insufficiency were eligible for inclusion. Quasi-randomized trials, observational studies and cross-over RCTs were excluded.

Interventions

Enteral feeding regimens were classified based on day of feed initiation, day of feed advancement and rate of feed advancement. The different enteral feeding strategies are provided in Table 1.

Outcomes

NEC stage \geq II (as per modified Bell's classification) or mortality before hospital discharge was the primary outcome evaluated.[13]

The secondary outcomes were –

NEC stage II or more, feed intolerance, time to establish full enteral feeding (defined as 120 - 150 ml/kg/day of enteral feeds), incidence of blood culture proven sepsis and mortality prior to hospital discharge.

Risk of bias assessment

The risk of bias was evaluated using the Cochrane Collaboration (London, UK) risk of bias tool 1.0 by two authors independently. Discrepancies were resolved by consulting a third author.

Data extraction, data synthesis and quality of evidence

Two authors extracted the data independently using a structured proforma. NMA was performed using a Bayesian Random effects model with vague priors using R-Software.[14-16] Generalized linear models with four chains, burn-in of 50,000 iterations, followed by 1,00,000 iterations and 10,000 adaptations were used. Network connectivity was evaluated using network plots. Gelman-Rubin plots, trace and density plots were inspected to look for model convergence. Model fit was assessed by leverage plots, total residual deviance and deviance information criterion. Node-splitting was performed to detect inconsistency between the direct and indirect fraction of evidence. Final estimates were reported as risk ratios (RR) [95% credible intervals (CrI)] and mean difference (MD) (95% CrI / CI). Network estimates for various comparisons were depicted using league plots and matrix plots. Interventions were ranked using the surface under the cumulative ranking curve (SUCRA) plots.[17]. SUCRA is a ranking system which ranks each intervention from 0 – 1. The closer is the SUCRA to 1, the better is the intervention. SUCRA values can vary for an intervention for different outcomes and must always be interpreted along with the certainty of the evidence. The GRADE approach for NMA was used to assess the certainty of evidence (CoE).[18]

Sensitivity analysis

Sensitivity analyses were performed based on:

- Gestational age
- Presence or absence of antenatal doppler abnormality
- Countries classified based on income level

Results

A total of 2,199 title and abstracts were screened after removing the duplicates and 102 full texts were retrieved for assessing their eligibility for inclusion. 39 studies enrolling 6982 neonates were included in the final synthesis.[8,19–56] (**Table 2**) The PRISMA flow is given in **Supplement Figure 1**. Nine authors of the included RCTs were contacted for additional information and five of them responded to our request. The mean birth weight of the studied neonates was 1094 grams. (**Suppl Fig. 2**) Twenty-three studies had enrolled neonates of gestational age ≤ 29 weeks', six studies had evaluated SGA neonates with evidence of placental insufficiency and twenty-three trials were from high income countries.

Risk of bias

While nineteen studies were classified as having a low risk of bias [8,19–25,27,28,31,33,36,37,40,41,45,47,48], nineteen studies were categorised as having a variable risk of bias for random sequence generation and allocation concealment. [26,29,30,32,34,35,38,39,42–44,46,49–55] None of the RCTs had blinded the intervention to the care providers due to the nature of the intervention. Ten trials had blinded the assessment of NEC. [8,19,20,23,35,36,40,45,46,55] Two trials had a high risk of attrition bias. [44,52] The risk of bias summary and risk of bias graph is given in **Supplement figure 3**.

Primary outcome (NEC stage \geq II or mortality)

A total of 37 studies enrolling 6593 preterm neonates with an event rate of 14.5% had reported on the primary outcome. The network plot is given in **Figure 1A**. The characteristics of the network for the primary outcome as well as other outcomes is given in **Supplement Table 2**. Early initiation with moderately early or late advancement using moderate volume increment enteral feeding regimens (EIMAMoV and EILAMoV) appeared to be most efficacious in decreasing the risk of NEC or mortality, while early initiation and early advancement with small volume increment regimen (EIEASV) was the least effective. [RR (95% CrI) - 0.39 (0.12, 0.95); 0.34 (0.10, 0.86)] (GRADE - Very low). The aforementioned two regimens namely, EIMAMoV and EILAMoV resulted in lesser incidence of the primary outcome when compared to various other feeding regimens as well. SUCRA ranked EILAMoV (SUCRA - 0.85), EIMAMoV (SUCRA - 0.79) as the two most efficacious feeding regimens in decreasing the risk of NEC or mortality. The SUCRA plots with SUCRA values for the various feeding strategies is given **Figure 1C**. Also, amongst early initiated feeding regimens which had used small volume increments, those that had advanced to nutritive feeds moderately early or late resulted in lesser incidence of NEC or mortality when compared to those that had advanced early in post-natal life. (GRADE – Very low). The forest plot with network estimates of various regimens is depicted in **Figure 1B**. The league plot illustrating the network estimates for the various comparisons is given in **Figure 2**.

The quality of evidence / GRADE for the various comparisons for the primary outcome and various secondary outcomes is given in **Table 3**. The pair-wise meta-analyses / direct evidence for the different enteral feeding strategies is given in **Figure 3**. Evaluation for inconsistency between the direct and indirect evidence is given **Supplement Figure 4**.

Secondary outcomes

NEC stage \geq II

Early initiation with early advancement of feeds using large volume increments (EIEALV) resulted in an increased risk of NEC when compared to multiple other feeding regimens.

(Suppl Fig. 5 – 8)

Mortality

Inconsistency was detected in the network for some of the comparisons for this outcome. None of the enteral feeding strategies resulted in a statistically significant difference in mortality.

(Suppl Fig. 9 – 12)

Feed intolerance

The network was not connected and network estimates could not be derived. The direct evidence from pair-wise comparisons revealed that regimens that initiated enteral feeds relatively early and advanced to nutritive feeding early or moderately early resulted in lesser feed intolerance when compared to late initiation and late advancement regimens. The direct evidence for these comparisons are given in **Suppl Fig. 13**

Sepsis

SUCRA ranked early total enteral feeding strategy (SUCRA - 0.89) as the best strategy in preventing sepsis. **(Suppl Fig. 14 – 17)**

Duration to full enteral feeds

The network estimates did not show any statistical difference between the various enteral feeding strategies. **(Suppl Fig. 18)** Node-splitting was not possible due to the sparseness of the network. The direct evidence from pair-wise meta-analyses showed that strategies with relatively earlier initiation, advancement and higher volume increments resulted in a significantly decreased days to full enteral feeds. **(Suppl Fig. 19)**

Sensitivity analyses for Primary outcome (NEC stage \geq II or mortality)

Neonates gestational age \leq 29 weeks'

None of the feeding interventions showed any statistically significant differences in reducing the primary outcome measure when compared to each other. **(Suppl Fig. 22 – 24)**

Neonates gestational age $>$ 29 weeks'

Early initiation with moderately early advancement using moderate volume increment (EIMAMoV) resulted in lesser incidence of NEC or mortality when compared to early initiation with moderately early advancement using large volume increment (EIMALV) [RR (95% CrI) - 0.24 (0.01, 0.89)] (GRADE – Low). **(Suppl Fig. 25)**

Neonates with no antenatal doppler abnormalities

Similar to the primary analysis, there was a trend towards early initiation with moderately early or late advancement using moderate volume increment enteral feeding regimens being more efficacious in decreasing the primary outcome measure. **(Suppl Fig. 26 – 27)**

Neonates who were small for gestational age with antenatal doppler abnormalities

Five of the six trials had reported on the primary outcome. Direct evidence from pair-wise meta-analysis did not show any statistically significant differences in the primary outcome measure between the different interventions. **(Suppl Fig. 28)**

Studies from high income countries

There were no statistically significant differences between any of the enteral feeding strategies in decreasing the risk of primary outcome measure when studies from high income countries were evaluated. **(Suppl Fig. 29 – 30)**

Studies from LMICs

The network was sparse and only direct evidence was evaluated. Moderate quality evidence showed that early initiation, moderately early advancement with moderate volume increment

(EIMAMoV) decreased the incidence of NEC or mortality when compared to a similar strategy but with earlier advancement to nutritive feeds (EIEAMoV) [RR (95% CI)- 0.25 (0.07 – 0.87)].

(Suppl Fig. 31)

Discussion

In this SR, we investigated different enteral feeding strategies for very preterm neonates with the primary outcome evaluated being NEC \geq stage II or mortality before discharge. Sixteen enteral feeding strategies were analysed, synthesizing data from 39 trials enrolling 6982 neonates in a NMA.

While early initiated (within 72 hours), moderately early (72 hours - 7 days) or late advanced (> 7 days) and moderate volume increment (20 - < 30 ml/kg/d) strategies, EIMAMoV and EILAMoV were the two most effective strategies to decrease the incidence of NEC or mortality; early initiated, early advanced (< 72 hours) and small volume advancement regimen (< 20 ml/kg/day), EIEASV was the least effective. Whilst our analysis revealed early initiated feeding strategies to be better than later ones, Morgan et al (2013) in their SR and pair-wise meta-analysis of early trophic feeds (introduced before 96 hours of age and continued for atleast until one week after birth) versus enteral fasting did not find any difference in the incidence of NEC or mortality.[6] This could be explained by the inclusion of recent studies in our review.

In a subsequent SR by Morgan et al (2014) comparing early introduction (day 1 – day 4) vs. delayed introduction of progressive feeds ($> \text{day } 4$, no upper limit defined) no difference was found between the two strategies in preventing NEC or mortality, which was contrary to our findings.[5] The discrepancy between our results and that of Morgan et al.'s might be explained by the differences in the way interventions were classified. Whilst our SR classified the progressive advancement period into three time periods, Morgan et al. had done so into two. Our results suggest that moderate volume advancement strategies might be superior to both

small as well as large volume advancement ones. The Cochrane review by Oddie et al (2017) revealed no differences between small (≤ 24 ml/kg/day) and large volume increments (> 24 ml/kg/day).[9] Our SR classified the feeding regimens in a multifaceted manner with two other aspects of enteral feeding namely, day of initiation and advancement of feeds besides volume of increment.

Both EIMAMoV and EILAMoV decreased the rates of NEC or mortality when compared to EIEAMoV. Also, the other early initiated, early advancement regimen with large volume increment, EIEALV resulted in higher incidence of NEC when compared to multiple others. There is a possibility that faster advancement of enteral feeds in early postnatal life might increase the metabolic demand on the gut as well as bacterial overgrowth subsequent to undigested feeds, increasing the risk of NEC.[57,58] The two late initiated and late advanced regimens, LILAMoV and LILASV decreased the risk of NEC without decreasing the rates of the combined outcome of NEC or mortality. There is a possibility of this being due to an increased risk of mortality with these two regimens.

Our review had pragmatic inclusion criteria, evaluating neonates with differing sickness profile, treated in NICUs with varying resources and survival rates. We tried to address this through sensitivity analyses. The results were similar to the primary analysis when neonates with no antenatal doppler abnormalities were evaluated separately. However, none of the feeding regimens resulted in better outcomes in neonates of ≤ 29 weeks, those with antenatal doppler abnormalities, and those from high income nations. Our sensitivity analyses revealed EIMAMoV to be better than EIMALV in neonates of > 29 weeks', and than EIEAMoV in neonates from LMIC.

Analysis of the secondary outcomes indicate that feeding regimens with relatively earlier initiation, earlier advancement and larger volume increments were better in decreasing the risk of feed intolerance, the duration to full feeds and sepsis. One novel feeding strategy, ETEF

which was evaluated by two trials in neonates of birth weight 1000-1500 grams, appeared most effective in preventing LOS. Such a regimen that can lower the incidence of LOS might have a huge impact in LMICs, where the burden of LOS with significant anti-microbial resistance (AMR) and sepsis related mortality is a cause of major concern.[59] A large multi-centric RCT (FEED1 trial) evaluating ETEF strategy is ongoing.[1]

Our SR has several limitations. To capture a wide variety of trials and interventions, we used broad inclusion criteria. Inconsistency was detected in some of the networks assessing the secondary outcomes. The network was sparse for some other secondary outcomes, for which our analysis and interpretation relied on direct fraction of the evidence from pair-wise meta-analysis. Finally, we had enrolled studies spanning three decades during which certain other proposed NEC prevention strategies, such as exclusive human milk diet and probiotics, were not a standard of care.

Conclusions

In preterm neonates of ≤ 32 weeks' gestational age:

- Early initiated (within 72 hours), moderately early (72 hours - 7 days) or late advanced (> 7 days) with moderate volume increment (20 - < 30 ml/kg/d) enteral feeding regimens (EIMAMoV, EILAMoV) were the two most efficacious in reducing the risk of NEC stage \geq II or mortality (CoE - Very low).
- The CoE being very low for the primary outcome, we suggest adequately powered, multi-centric RCTs evaluating these two regimens in future.

Acknowledgement

We acknowledge the contributions of Prof Sushma Nangia and Dr Kenny McCormick in giving intellectual inputs during the writing of the manuscript. We also thank Abdul Kareem Pullattayil S for devising the literature search strategy for all the databases and Dr Roseanna Harrison and Dr Debasish Nanda for assisting in proofreading of the final version of the manuscript. We thank Prof David C Wilson, Dr Pamela Cairns, Prof RM van Elburg, Associate Prof Shmuel Arnon and Dr M Gharehbaghi for providing additional information related to their studies. We are also grateful to Dr Roya Taheritafti for translating a study from Persian to English.

Statement of Ethics: Not applicable

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Funding Sources: None

Author Contributions

Dr Viraraghavan Vadakkencherry Ramaswamy, Dr Tapas Bandyopadhyay and Dr Prathik Bandiya conceptualized the systematic review and did the data analysis. Dr Javed Ahmed and Dr Tapas Bandyopadhyay were responsible for literature search and data extraction. Dr Sanja Zivanovic provided a first draft of the manuscript. Prof Charles Christoph Roehr gave further intellectual inputs and revised the initial draft. All authors approved the final version for submission and agree to be accountable for all aspects of the work.

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Figure Legends

Fig. 1 -

- A. Network plot for the primary outcome - NEC stage \geq II or mortality
- B. SUCRA plot with SUCRA values (%) for the primary outcome of NEC stage \geq II or mortality
- C. Forest plot depicting the network estimates [RR (95% CrI)] of the various interventions with 'EIEASV' as the common comparator for the primary outcome of NEC stage \geq II or mortality

Fig. 2 - League plot depicting the network estimates [RR (95% CrI)] of different enteral feeding strategies for the primary outcome of NEC stage \geq II or mortality

Fig. 3 - Direct evidence from the pair wise comparisons for the primary outcome NEC stage \geq II or mortality

