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Early Exclusive Enteral Feeding Versus Gradual Advancement in Preterm Infants:

A Systematic Review and Meta-Analysis of Randomized Clinical Trial

Alimentação Enteral Exclusiva Precoce Versus Avanço Gradual em Recém-Nascidos Prematuros: Uma Revisão Sistemática e Metanálise de Ensaios Clínicos Randomizados

Goiânia - GO

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GUILHERME DE ALMEIDA TELES

VÍCTOR RAMOS PERDOMO VIEIRA

Early Exclusive Enteral Feeding Versus Gradual Advancement in Preterm Infants: A Systematic Review and Meta-Analysis of Randomized Clinical Trial

Alimentação Enteral Exclusiva Precoce Versus Avanço Gradual em Recém-Nascidos Prematuros: Uma Revisão Sistemática e Metanálise de Ensaios Clínicos Randomizados

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ATA DE DEFESA DE TRABALHO DE CONCLUSÃO DE CURSO

Ao décimo dia do mês de junho do ano de dois mil e vinte e seis iniciou-se a sessão pública de defesa do Trabalho de Conclusão de Curso (TCC) intitulado "Early exclusive enteral feeding versus gradual advancement in preterm infants: a systematic review and meta-analysis of randomized clinical trial", de autoria de Victor Ramos Perdomo Vieira e Guilherme de Almeida Teles, do curso de Medicina, da Faculdade de Medicina da UFG. Os trabalhos foram instalados pelo Prof. Solomar Martins Marques (FM/UFG) com a participação dos demais membros da Banca Examinadora: Profa. Eliane Terezinha Afonso (FM/UFG) e Prof. Flávio Henrique Alves de Lima (FM/UFG). Após a apresentação, a banca examinadora realizou a arguição dos estudantes. Posteriormente, de forma reservada, a Banca Examinadora atribuiu a nota final de (10.0) , tendo sido o TCC considerado (Aprovados).

Proclamados os resultados, os trabalhos foram encerrados e, para constar, lavrou-se a presente ata que segue assinada pelos Membros da Banca Examinadora.

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Resumo

Introdução: Os recém-nascidos prematuros apresentam alto risco de complicações relacionadas à imaturidade gastrointestinal, incluindo enterocolite necrosante (ECN) e intolerância alimentar. A estratégia ideal de alimentação enteral ainda é incerta. **Metodologia:** Foi realizada uma meta-análise comparando a alimentação enteral exclusiva precoce com o avanço gradual da alimentação enteral. As bases de dados PubMed, Embase e Cochrane foram pesquisadas, e foram calculados os riscos relativos (RR) e as diferenças médias (DM), com intervalos de confiança de 95%. **Resultados:** Foram analisados sete estudos, totalizando 2.649 recém-nascidos prematuros. Não foram observadas diferenças significativas para ECN (RR 0,88; p=0,77) nem para intolerância alimentar (RR 0,82; p=0,48). A alimentação enteral exclusiva precoce mostrou-se associada a uma menor duração da internação hospitalar (DM −4,81 dias; p=0,03) e a uma redução no uso de fluidos intravenosos (DM −3,19 dias; p=0,02). **Conclusão:** A alimentação enteral exclusiva precoce parece ser segura e pode reduzir o tempo de internação e a exposição a fluidos intravenosos em recém-nascidos prematuros.

Palavras chaves: Recém-nascidos prematuros; Enterocolite necrosante; Alimentação enteral.

Abstract

Introduction: Preterm infants are at high risk of complications to gastrointestinal immaturity, including necrotising enterocolitis (NEC) and feeding intolerance. The optimal enteral feeding strategy remains uncertain. **Methodology:** A meta-analysis compared early exclusive enteral feeding with gradual enteral feeding advancement. PubMed, Embase, and Cochrane were searched. Risk ratios (RR) and mean differences (MD) with 95% confidence intervals were calculated. **Results:** Seven studies including 2,649 preterm infants were analysed. No significant differences were observed for NEC (RR0.88; p=0.77) or feeding intolerance (RR0.82; p=0.48). Early exclusive enteral feeding appeared associated with shorter hospital stay (MD −4.81 days; p=0.03) and reduced intravenous fluid use (MD −3.19 days; p=0.02). **Conclusion:** Early exclusive enteral feeding appears safe and may reduce hospitalisation and intravenous fluid exposure in preterm infants.

Key words: Preterm Infants; Necrotising enterocolitis; Enteral feed.

1. INTRODUCTION

Preterm birth, defined as delivery before 37 weeks of gestation, remains a major global health challenge. Among the main concerns in the management of these patients is physiological immaturity, which compromises clinical stability and may negatively influence long-term outcomes (1,2). In this context, the establishment of adequate nutritional support represents a fundamental component of neonatal care, as it can substantially reduce morbidity and mortality in this vulnerable population (3).

It is well established that the introduction of enteral feeding, particularly when implemented early, provides physiological stimulation for gastrointestinal tract maturation, which is associated with protective effects on the microbiota and a reduction in complications related to dependence on parenteral nutrition (4,5). However, specialists commonly adopt a gradual advancement strategy of enteral feeding volumes supplemented with parenteral nutrition due to the potential risk of developing feeding intolerance and necrotizing enterocolitis, a critical gastrointestinal inflammatory condition affecting newborns (6).

This clinical dilemma, which balances nutritional optimization with patient safety, has led to substantial variability in feeding practices across neonatal intensive care units. Current evidence demonstrates conflicting results regarding the comparative superiority of feeding strategies. Many of these studies are limited by small sample sizes, heterogeneity in feeding protocols, and differences in baseline risk profiles, resulting in persistent uncertainty in the literature (7).

A previous Cochrane systematic review published in 2020 analyzed infants with birth weights between 1000 and 1500 grams without restrictions regarding gestational age and found that the intervention reduced hospital length of stay without increasing complications. However, the review included a limited number of studies, all of which were single-centertrials conducted in India, which restricts the generalizability of the findings to populations in other healthcare settings (7).

Therefore, we conducted a systematic review and meta-analysis to compare early full enteral feeding (defined as 60–80 mL/kg/day via the enteral route without or with minimal use of intravenous fluids or parenteral nutrition for a short period of time) with a gradual advancement strategy (defined as minimal enteral feeding 20–30 mL/kg/day

associated with intravenous fluids or parenteral nutrition, with gradual increases) in preterm infants (<37 weeks). We performed a quantitative analysis including only randomized studies to evaluate the potential effects of these feeding strategies on clinical outcomes in preterm infants.

2. METHODS

This systematic review and meta-analysis was performed in accordance with the Cochrane Collaboration Handbook for Systematic Review of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.(8,9). The study protocol was registered in the International Prospective Register of Systematic Reviews under the registration number CRD420261327511

2.1 - Eligibility Criteria

Inclusion in this systematic review and meta-analysis will be restricted to studies that meet all of the following eligibility criteria: (1) randomized clinical trials; (2) comparing early exclusive enteral feeding – defined as high initial enteral feeding volumes (60–80 mL/kg/day) since the first days of life, with absent or minimal use of intravenous fluids or parenteral nutrition – to gradual enteral feeding advancement – defined as low initial enteralfeeding volumes 20–30 mL/kg/day, with remaining nutritional support supplemented with intravenous fluids or parenteral nutrition. Although they differed in the initial enteral volume provided, both approaches gradually advanced as tolerated until reaching a final enteral nutritional target of 150–180 mL/kg/day (Table 1); (3) conducted in hemodynamically stable preterm infants (reported gestational age <37 weeks, presented either as a direct value or as mean ± standard deviation); and (4) reporting at least one predefined outcome of interest, including necrotizing enterocolitis, sepsis, feeding intolerance, time to achieve full enteral feeding, time to regain birth weight, duration of intravenous fluids, or length of hospital stay.

2.2 - Search strategy and data extraction

We systematically searched PubMed, Embase and Cochrane Central Register of Controlled Trials from inception to February 2026. Key terms included “Infant, Premature,” “Low Birth Weight Infant,” “Very Low Birth Weight Infant,” “enteral nutrition,” “early enteral feeding,” “exclusive enteral feeding,” “parenteral nutrition,” “minimal enteral nutrition,” and “trophic feeding,” with filters for randomized controlled trials. The full search strategy is provided in the Supplementary Material.

All records identified through the search strategy will be imported into Zotero 6.0 (Corporation for Digital Scholarship, Roy Rosenzweig Center for History and New Media, George Mason University, Fairfax, Virginia, United States of America), and duplicates will be removed. The reference lists of all included studies and relevant systematic reviews will be manually screened to identify any additional eligible trials. Two reviewers (G.T. and V .P), using Rayyan (Qatar Computing Research Institute, Doha, Qatar) will independently screen titles and abstracts, assess full texts for eligibility, and extract data according to the predefined inclusion and exclusion criteria. Any disagreements will be resolved by discussion and consensus.

The following information will be extracted from the included studies: number of participants and baseline characteristics (e.g., gestational age, birth weight, proportion of very low birth weight infants, sex distribution, and relevant clinical variables); detailed description of the feeding strategies in intervention and control groups; type of milk administered precisely at the time of the intervention or control procedure; criteria for feeding progression; and use and duration of parenteral nutrition or intravenous fluids. Maternal characteristics will also be extracted, including maternal age, proportion of cesarean deliveries, and use of antenatal corticosteroids. Reported clinical outcomes will be extracted, including necrotizing enterocolitis, sepsis, feeding intolerance, time to achieve full enteral feeding, time to regain birth weight, duration of intravenous fluids, and length of hospital stay.

2.3 - Endpoints and subgroup analysis

The predefined endpoint analyzed as the primary outcome will be risk of necrotizing enterocolitis in preterm infants receiving early exclusive enteral feeding compared with gradual feeding advancement. Secondary outcomes will include differences in incidence of overall sepsis; feeding intolerance; time to achieve full enteral feeding; time to regain

birth weight; duration of intravenous fluids; and length of hospital stay. Despite their great relevance, it was not possible to assess neurocognitive outcomes due to a lack of data among the included studies.

Given the limited number of studies and low methodologic certainty of the evidence, an exploratory subgroup analysis was conducted according to the type of milk used duringthe intervention for the primary outcome of NEC, with studies categorized into a mixed feeding group (human milk plus formula) and an exclusive human milk group. These analyses should be interpreted with caution and should not be extrapolated.

2.4 - Assessment of the risk of bias

Two reviewers (G.T. and V .P.) independently evaluated the risk of bias of the included studies, and any discrepancies were resolved by consensus between the two reviewers. Randomized controlled trials were assessed using the Cochrane Collaboration’s Risk of Bias tool for randomized trials (RoB 2), which evaluates five domains: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results

2.5 - Assessment of publication bias

Due to the limited number of studies included in the meta-analysis, only an exploratory and qualitative analysis of the possibility of publication bias was performed. For this purpose, the asymmetry in the funnel plot was evaluated. Quantitative tests such as Egger's regression test were not feasible due to the insufficient number of articles, as recommended by methodological guidelines.(8,9)

2.6 - Sensitivity analysis

Due to the high heterogeneity (>90%), we performed leave-one-out sensitivity analyses for length of hospital stay, duration of intravenous fluid administration, time to birth weight recovery, and time to enteral nutrition initiation, in order to assess the effects of influential studies in the pooled analysis and in the dispersion among nutritional protocols.Studies were sequentially removed, one at a time, and the data were reanalyzed to ensure the stability of the pooled effects.

An exploratory sensitivity analysis including studies that reported NEC was performed, restricting the evaluation of primary outcome to specific high-risk populations. We assessed the primary outcome exclusively among infants with very low birth weight (<1500g) and those with a gestational age ≤ 33 weeks. These results should be interpreted with caution.

2.7 - GRADE assessment

Two independent reviewers (G.T. and V .P.) assessed the level of certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool, and disagreements were resolved by consensus. The domains evaluated were risk of bias, inconsistency, indirectness, imprecision, and publication bias. (10)

2.8 - Statistical analysis

Risk ratios (RR) with corresponding 95% confidence intervals (CI) will be calculated for dichotomous outcomes, while mean differences (MD) with 95% CIs will be used for continuous variables. When a specific study (Jajoo, et. al; Nangia, et. al; Razzaghy, et. al) reported continuous data as median and interquartile range (IQR), we first assessed whether there was evidence of substantial skewness. In the absence of significant asymmetry, the data were converted to mean and standard deviation using the methods described by Wan et al. and Luo et al..(11,12) In addition, when standard deviations were not reported, they were derived from reported confidence intervals, assuming equal variances between groups, inaccordance with Cochrane Handbook. Given the expected clinical and methodological variability among the included trials, a random-effects model will be employed.

Statistical heterogeneity will be evaluated using the I^2 statistic and the Cochrane Q (chi-square) test. A p-value <0.10 in the Q test and an I^2 value greater than 25% will be considered indicative of significant heterogeneity. Review Manager (RevMan Web; Cochrane, London, United Kingdom) was used as software to perform all statistical analyses.

3. RESULTS

3.1 - Study selection and characteristics

The initial search yielded 2458 results. After removal of duplicates and ineligible studies, as detailed in Figure 1, 24 records were selected for full-text review. Of these, 7 randomized controlled trials were included in this systematic review and meta-analysis, based on eligibility criteria.(13,14,15,16,17,18,19)

A total of 2,649 preterm infants were included across the analyzed studies, with 1,329 (50%) allocated to Early Total Enteral Nutrition and 1,320 (50%) to Gradual Advancement. Mean gestational age ranged approximately from 31.0 to 35.5 weeks in the Early group and from 30.3 to 34.8 weeks in the Gradual group. Mean birth weight ranged from 1,323 g to 1,708 g in the Early group and from 1,305 g to 1,732 g in the Gradual group. The proportion of small for gestational age infants varied between 5.7% and 64.7% in the Early group and between 4.0% and 59.6% in the Gradual group. Maternal age was generally comparable between groups when reported, and the proportions of cesarean delivery and antenatal corticosteroid use were also similar across intervention arms. Overall, baseline neonatal and maternal characteristics were comparable between the Early and Gradual feeding groups (Table 1).

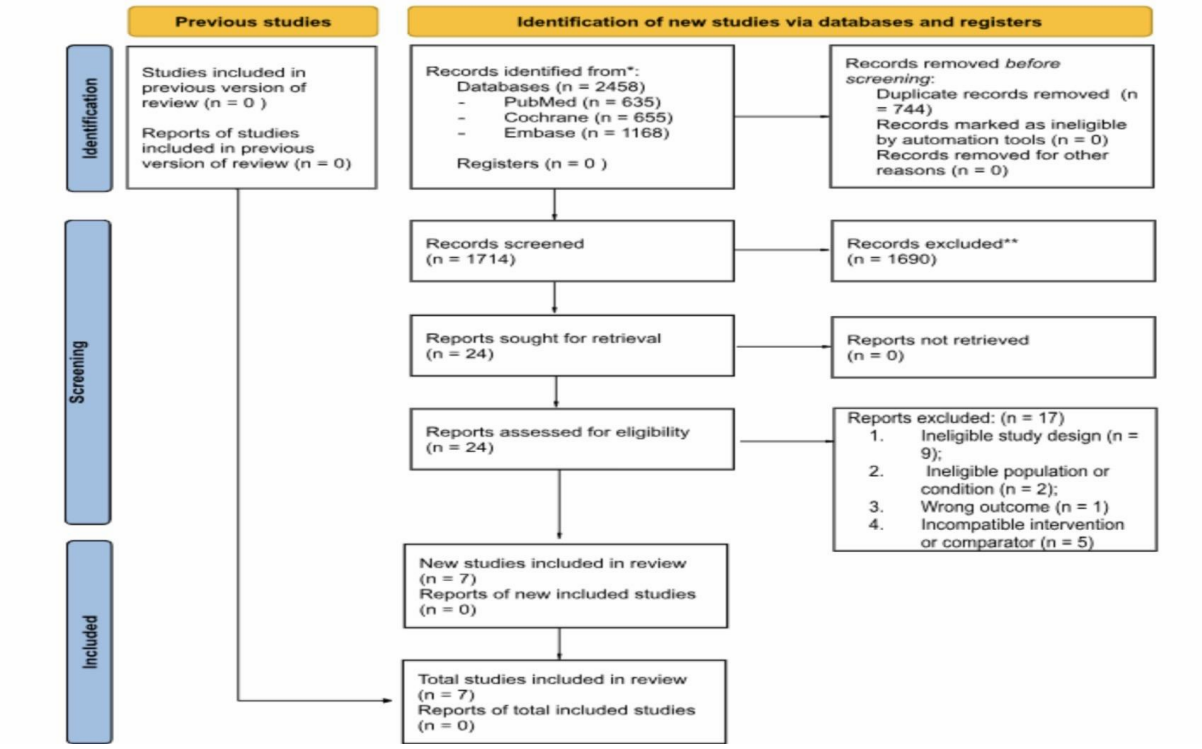

Figure 1: PRISMA flow diagram of estudy screening and selection

3.2 - Pooled analysis of all studies

The pooled analyses suggested no statistically significant difference between early exclusive enteral feeding regarding NEC (RR 0.88; 95% CI 0.39-1.98; p=0.77; I2=0%; Figure 2), time to achieve enteral feed (MD -1,89 days; 95% CI -4.14-0.45; p=0.08; I2=98%; Supplementary Figure S1) and feed intolerance (RR 0.82; 95% CI 0.41-1.65; p=0.48; I2=41%; Figure 3). Similarly, early exclusive enteral feeding did not appear to be clearly associated with differences in sepsis rates (RR 0.68; 95% CI 0.29-1.58; p=0.27; I2=63%; Supplementary Figure S2) and time to regain birth weight (MD -2.10 days; 95% CI -5.75-1.56; p=0.19; I2=98%; Supplementary Figure S3).

However, pooled analyses suggested a possible reduction in length of hospital stay of approximately five days (MD −4.81 days; 95% CI −9.00 to −0.61; p = 0.03; I^2 = 94%; Figure (4) and in duration of intravenous fluid use by about three days (MD −3.19 days; 95% CI −5.37 to −1.01; p = 0.02; I^2 = 95%; Figure 5) among infants receiving early total enteral nutrition compared with the control group.

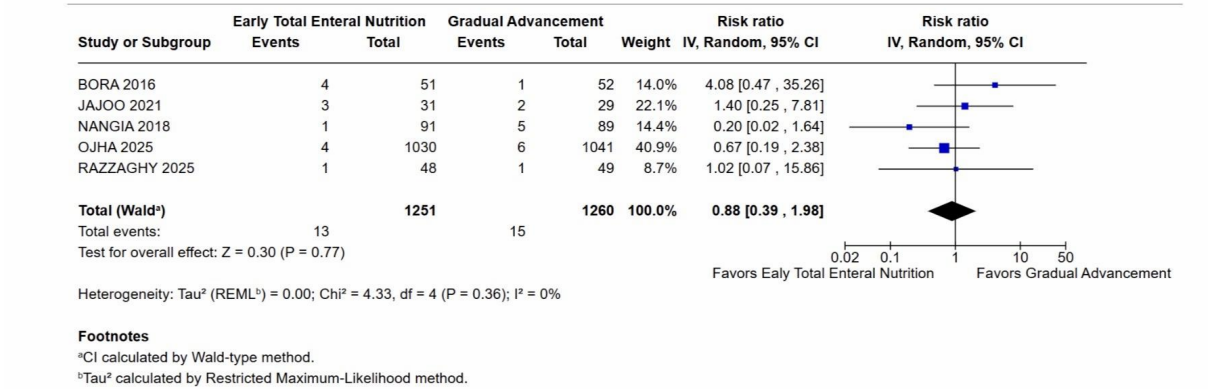

Figure 2 Necrotising enterocolitis - There was no statistically significant difference between groups (p=0.77)

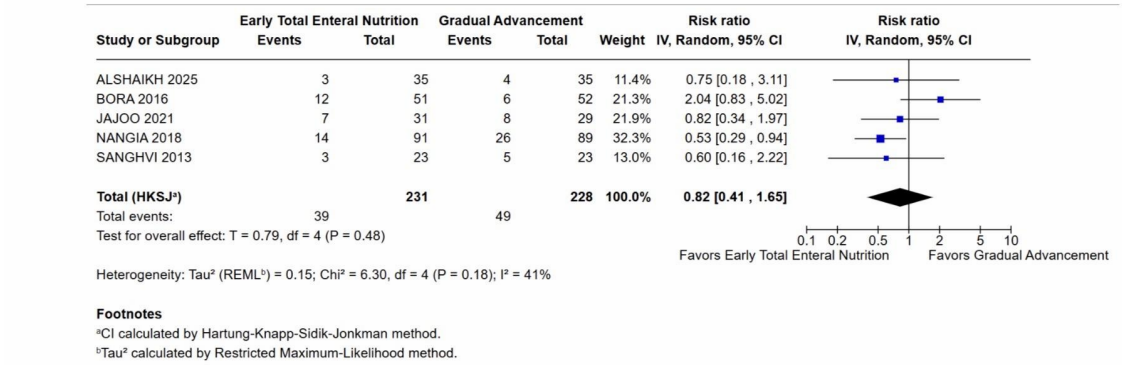

Figure 3 Feed intolerance - There was no statistically significant difference between groups (p=0.48)

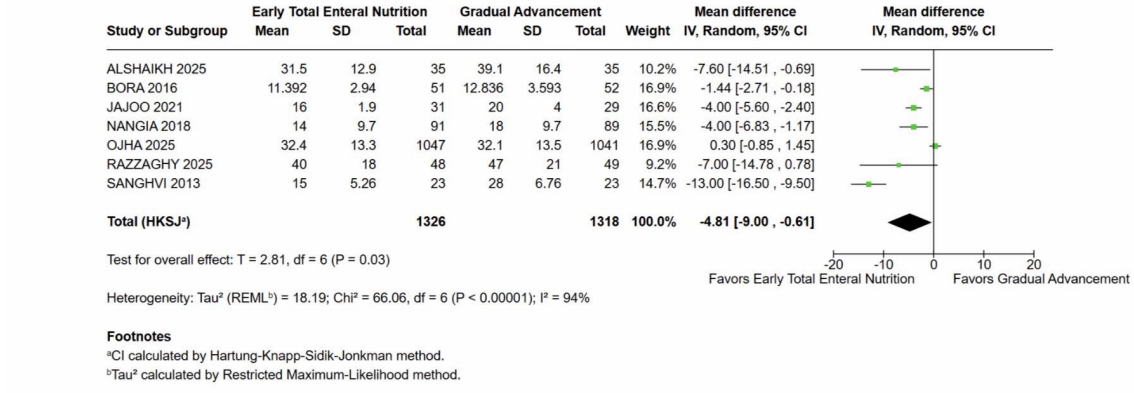

Figure 4 Length at hospital - Significantly lower in early total enteral nutrition (p=0.03)

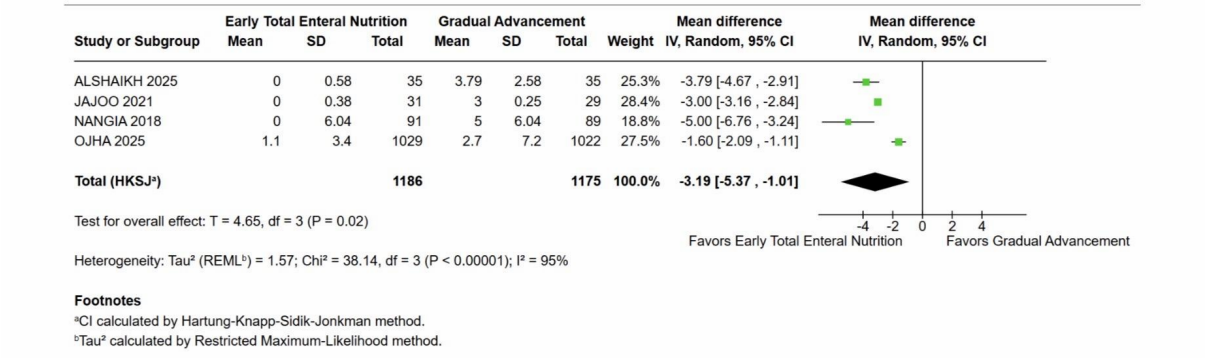

Figure 5 Duration of IV fluid - Significantly lower in early total enteral nutrition (p=0.02)

3.3 - Subgroup analyses

The exploratory subgroup analysis for NEC according to type of milk suggested no significant differences between early total enteral nutrition and gradual advancement in the mixed feeding subgroup (RR 0.66, 95% CI 0.26–1.65; p = 0.37) or in the exclusive human milk subgroup (RR 2.40, 95% CI 0.44–13.09; p = 0.31). The test for subgroup differences was not significant (p = 0.19). (Supplementary Figure S4).

3.4 - Risk of bias assessment

Most of the randomized clinical trials included in this meta-analysis were classified as low overall risk of bias using the RoB 2 tool. Only two articles were assessed as having some concerns. This was mainly due to the classification of some concerns in the domain bias in selection of the reported results. (Figure 6)

Figure 6 Risk of bias assessment

3.5 - Assessment of publication bias

Visual inspection of the funnel plot suggested slight asymmetry.(Figure 7)

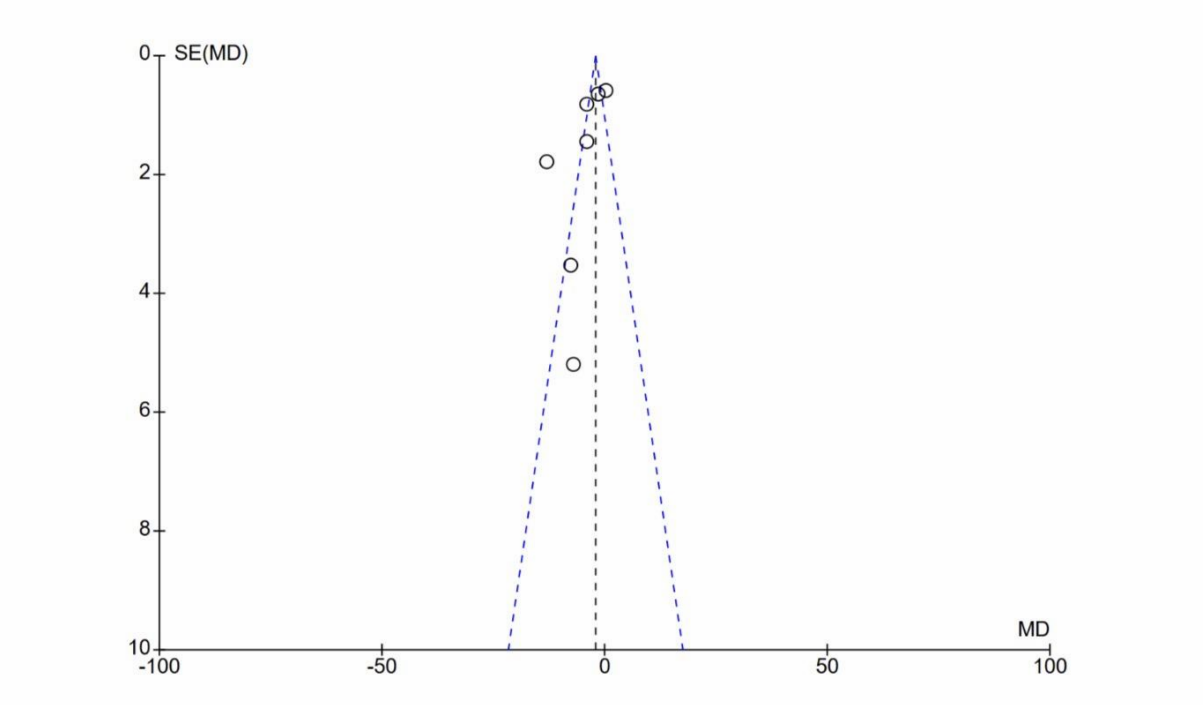

Figure 7 Funnel Plot

3.6 - Sensitivity analyses

The pooled sensitivity analysis of very low birth weight infants (1000–1500 g) suggested results consistent with the primary analysis. In this group, no statistically significant differences were observed between intervention and control for necrotizing enterocolitis (RR 1.05; 95% CI 0.03–42.47; p = 0.96; I^2 = 50%; Supplementary Figure S5). No statistically significant differences were observed for NEC in sensitivity analysis of gestational age ≤ 33 weeks (RR 0.88; 95% CI 0.34–2.28; p = 0.79; I^2 = 0%; Supplementary Figure S6).

In the leave-one-out sensitivity analysis for length of hospital stay and time to achieve enteral feed, the overall effect was found to be unstable. These findings indicate that the results are sensitive to the exclusion of individual studies. For the outcomes of time to regain birth weight, revealed consistent results after omitting each individual study. The results for the sensitivity analyses are presented in Supplementary Figures S7, S8 and S9

3.7 - GRADE assessment

The certainty of evidence for the outcomes varied for the results. The results for necrotizing enterocolitis had a moderate certainty of evidence. For feed intolerance and sepsis had a low certainty of evidence. Time to full enteral feeding, time to regain birth weight, hospital stay, and time to stop intravenous fluids, had a very low certainty of evidence, which revealed a trend towards early total enteral nutrition; however, these results had a high heterogeneity and wide confidence intervals.(Supplementary Figure S10).

4. Discussion

In this systematic review and meta-analysis including 7 randomized clinical trials, encompassing a total of 2,649 preterm infants (<37 weeks), early and exclusively enteral feeding was compared with gradual advancement supplemented with parenteral support. The main findings were the probable absence of statistically significant differences between the intervention and control groups for the outcomes of (1) NEC, (2) time to achieve enteral feed, (3) feed intolerance, (4) sepsis, and (5) time to regain birth weight. On the other hand, early total enteral nutrition appears to be associated with a reduction of approximately 5 days in length of hospital stay and about 3 days in the duration of IV fluid use compared with gradual advancement. These findings should be interpreted cautiously given the low to very low certainty of evidence for some outcomes and the substantial heterogeneity across studies.

The standard nutritional approach adopted for this population consists of introducing small volumes of enteral feeding supplemented with the use of intravenous fluids or parenteral nutrition, which would be our control group. This is due to concerns about the risk of highly morbid and mortal gastrointestinal complications, such as necrotizing enterocolitis,in the still immature gastrointestinal system.(4,20) International guidelines for the management of this population, such as those of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), suggest caution in the progression of enteral feeding for very small premature infants early in life.(21)

However, the interpretation of the results found in this meta-analysis suggests that, in practice, the early implementation of higher volumes of enteral feeding can constitute a safe alternative for the management of selected premature infants. This is mainly due to

the reduction in dependence on parenteral support and the length of hospital stay, without a significant increase in the risk of infectious and gastrointestinal complications. In this respect, the reduction in dependence on parenteral support, in turn, decreases exposure to invasive procedures, such as the insertion of venous catheters, contributing to faster clinical stabilization.(22) In addition, the reduction in the length of hospital stay also constitutes a factor in reducing the costs related to neonatal care.(23)

A meta-analysis of 14 randomized clinical trials compared early initiation of enteral feeding, performed before 72 hours of life, with late initiation, performed after 72 hours, in preterm or VLBW newborns. Overall, the combined analysis demonstrated that the intervention was associated with a reduction in mortality, a reduction in length of hospital stay, and a reduction in neonatal sepsis. Furthermore, no significant differences were found between the two groups regarding NEC and feeding intolerance. Although Chitale compared only the timing of the initiation of enteral feeding, his findings appears similar to those observed in the present meta-analysis, which evaluated different strategies for progression of feeding volume.(24) This suggests the potential safety of early enteral nutrition in preterm infants.

Another systematic review published in 2020 had a similar study design, comparing timing of introduction, volume, and food progression strategies, however, not restricting it to preterms. In general, it presented comparable results for the outcomes evaluated. (7) However, this review presents relevant methodological limitations, including a smaller number of studies, reduced samples, and single-center trials conducted exclusively in India, which restricts the generalizability of the results. High heterogeneity was also present for the outcomes assessed.(7) Given the emergence of new studies with wider geographic distribution and higher methodological quality, we conducted this meta-analysis to assess whether there are variations in the results found.

Although the FEED1 trial contributed substantially to the pooled sample size, sensitivity analyses demonstrated that the overall direction and magnitude remained consistent after exclusion of this study.

However, there are significant limitations that should be borne in mind while interpreting the above meta-analysis. Firstly, though using randomized clinical trials, the total number of studies included in the meta-analysis was small (n = 7). Secondly, significant heterogeneity was observed among the studies included in the meta-analysis with

respect to some of the continuous outcomes, such as time to full enteral nutrition, time to regain birth weight, and length of stay, which were high (>90%), suggesting that significant variability exists with respect to the type of feeding, the population studied, and clinical practices, including the criteria used to advance the type of milk used.(25,26) Persistent heterogeneity after leave-one-out analyses suggests that variability was multifactorial rather than driven by a single study.

None of the included studies evaluated long-term neurodevelopment outcomes, which is an important outcome for the follow-up of preterm infants. Therefore, the implications of each nutritional approach and its safety remain uncertain with regard to cognitive development.

Another consideration is that most trials included were single-center studies conducted in India and other middle-income settings. Differences in neonatal intensive care resources, baseline population and local feeding protocols may limit the applicability of these findings to high-income neonatal intensive care settings.

Among the methodological strategies adopted to minimize the identified limitations are the performance of sensitivity analyses using the leave-one-out method, the performance of subgroup analyses of risk groups such as VLBW newborns and gestational age ≤ 33 weeks. In addition, subgroup analysis was performed according to the type of milk used for the outcome of necrotizing enterocolitis and the certainty of evidence was determined using the GRADE system.(10) Some of these analyses showed combined effect instability, which indicates that the results obtained may be subject to the influence of the exclusion of individual studies.

The majority of the studies were classified as having a low risk of bias according to the RoB 2 tool. However, methodological limitations should be considered. None trials blinded caregivers which may have increased the risk of performance, particularly for subjective outcomes such as feed intolerance and feeding progression decisions.

The assessment using the GRADE system showed that, although early total enteral nutrition had some potential benefits in certain outcomes, these should be interpreted cautiously due to the limited strength of the available evidence. The strength of the available evidence varied across the outcomes, and some were downgraded due to

imprecision and heterogeneity in the studies. The assessment of publication bias was limited by the small number of included studies, although funnel plot inspection suggested slight asymmetry.

Therefore, although the results suggest that early total enteral nutrition may reduce the length of hospital stay and the amount of intravenous fluids without increasing the risks of gastrointestinal or infectious complications, the results should be interpreted with limitations in mind, and further multicenter RCTs with greater standardization of nutritional protocols and more heterogeneous samples are needed to strengthen the existing evidence base.

5. Conclusion

Early exclusively enteral nutrition may represent a viable alternative for selected preterm infants. Available evidence suggests a possible reduction in hospital stay and intravenous fluid use time without, however, suggesting a clear increase in the risk of substantial complications such as NEC and mortality. Further multicenter randomized studies with larger geographic representation and standardized nutritional protocols are warranted to improve the external validity and reduce the limitations of this meta-analysis.

6. References

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7. Appendix

7.1 - Complete research strategy:

("Infant, Premature"[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Infant, Very Low Birth Weight"[Mesh] OR preterm infant*[tiab] OR premature infant*[tiab] OR preterm neonate*[tiab] OR premature neonate*[tiab] OR very low birth weight infant*[tiab] OR VLBW infant*[tiab]) AND ("Enteral Nutrition"[Mesh] OR enteral feeding[tiab] OR early enteral feeding[tiab] OR early enteral nutrition[tiab] OR exclusive enteral feeding[tiab] OR full enteral feeding[tiab] OR first day feeding[tiab] OR day 1 feeding[tiab] OR immediate enteral feeding[tiab] OR feeding from birth[tiab]) AND ("Parenteral Nutrition"[Mesh] OR "Feeding Methods"[Mesh] OR gradual feeding[tiab] OR progressive feeding[tiab] OR delayed enteral feeding[tiab] OR slow feeding advancement[tiab] OR trophic feeding[tiab] OR minimal enteral nutrition[tiab] OR partial parenteral nutrition[tiab] OR intravenous fluids[tiab]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trials as topic[mesh:noexp] OR trial[ti] OR random*[tiab] OR placebo*[tiab]).

7.2 - Figures Supplementary

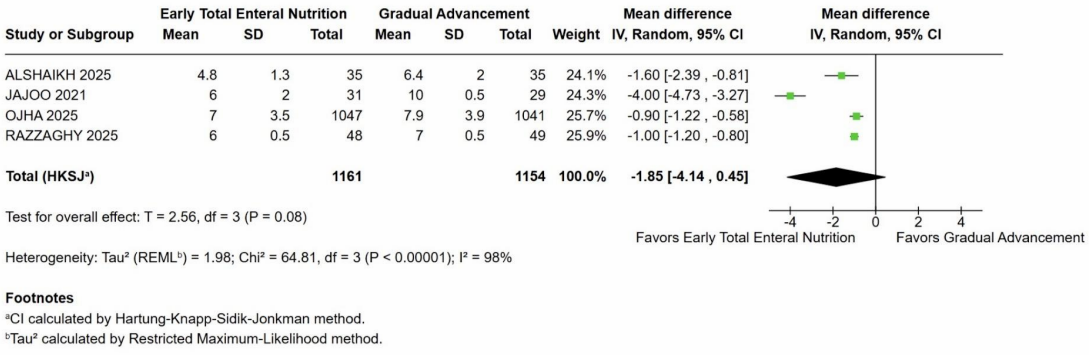


Figure S1 Time to achieve enteral feed - There was no statistically significant difference between groups (p=0,08)

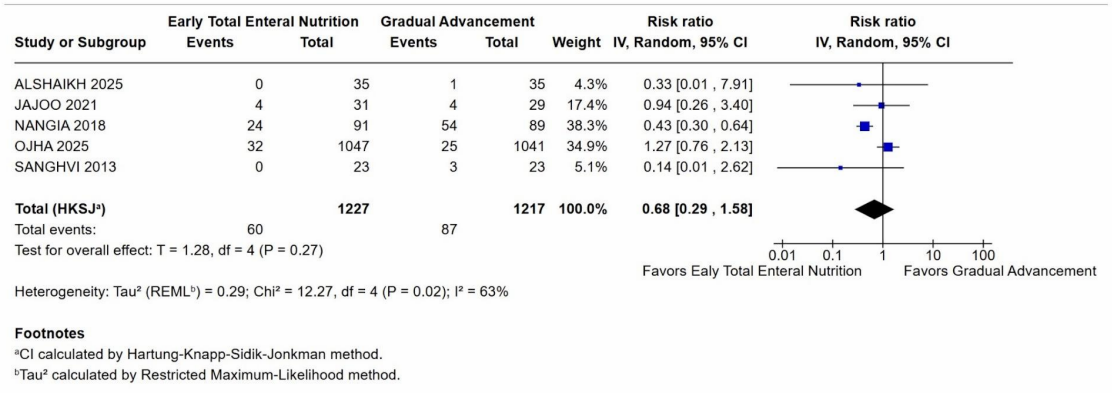


Figure S2 Sepsis - There was no statistically significant difference between groups (p=0,27)

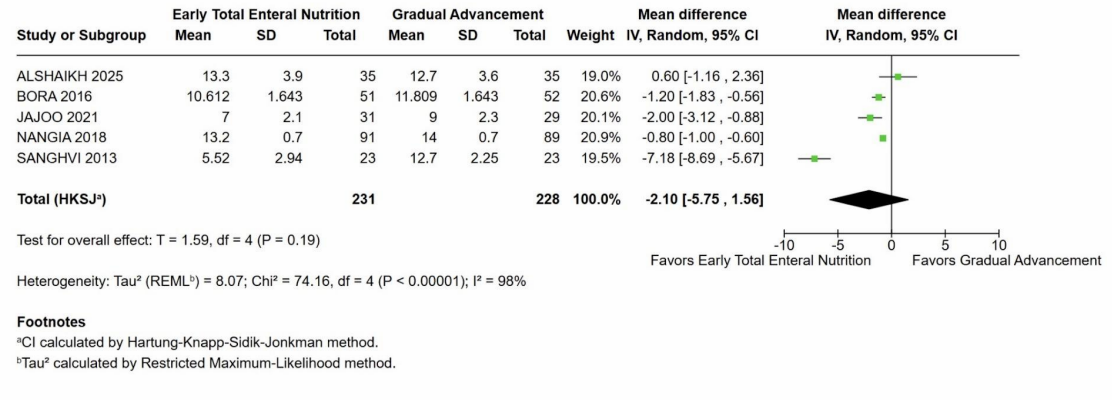


Figure S3 Time to regain birth weight - There was no statistically significant difference between groups (p=0,19)

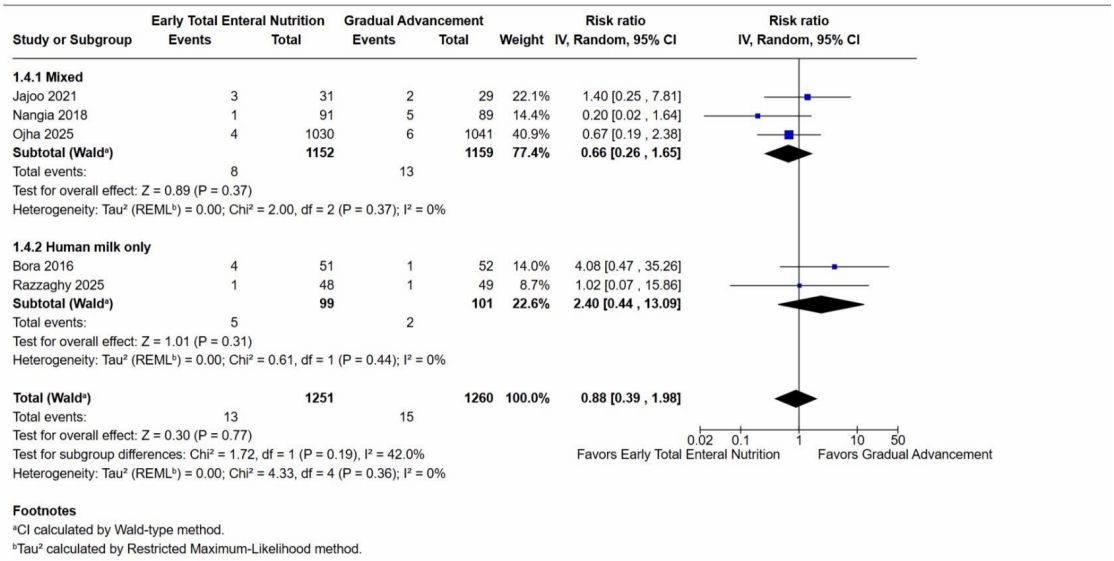


Figure S4 Type of milk subgroup - There was no statistically significant difference between subgroups for NEC (p=0,19)

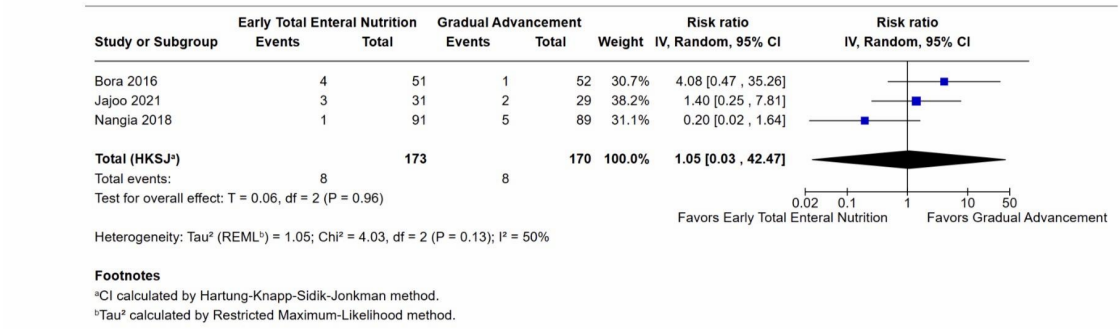


Figure S5 Sensitivity analysis of very low birth weight - There was no statistically significant difference between groups for NEC (p=0,96)

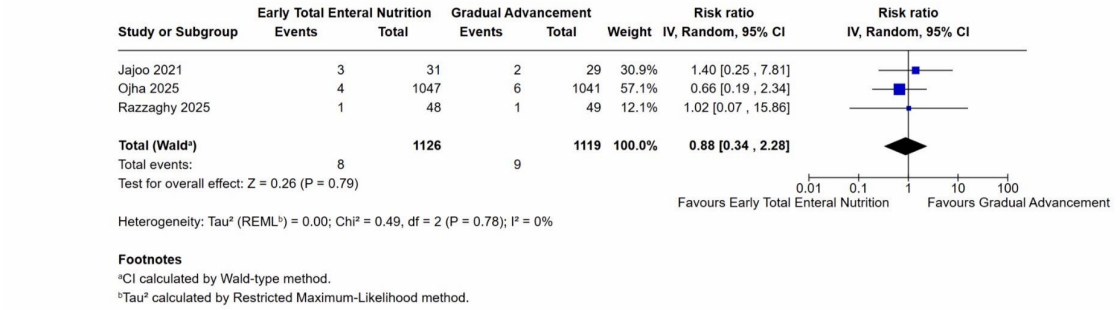
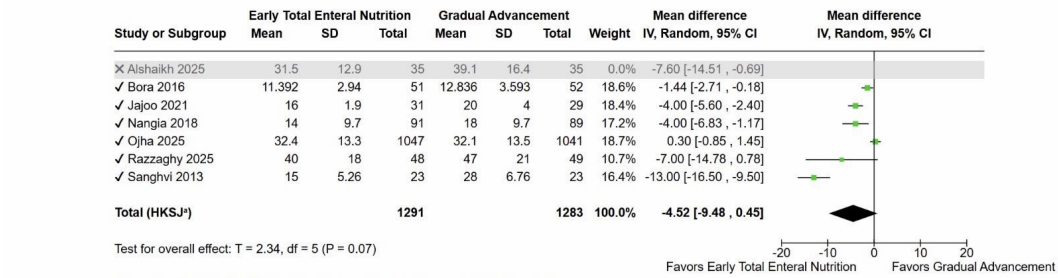


Figure S6 Sensitivity analysis of gestational age ≤ 33 weeks - There was no statistically significant difference between groups for NEC (p=0,79)



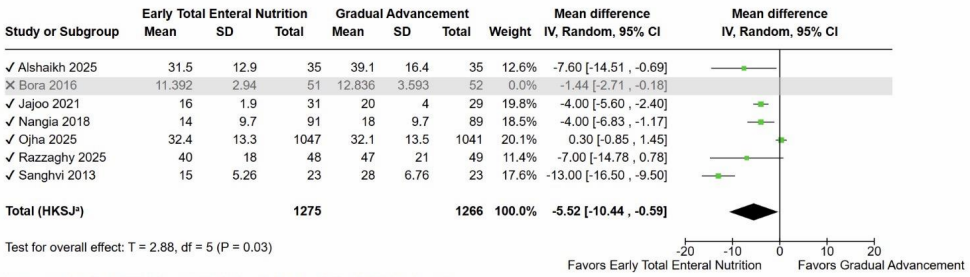
Test for overall effect: T = 2.34, df = 5 (P = 0.07)

Heterogeneity: Tau² (REML[b]) = 20.07; Chi² = 63.53, df = 5 (P < 0.00001); I² = 96%

Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.



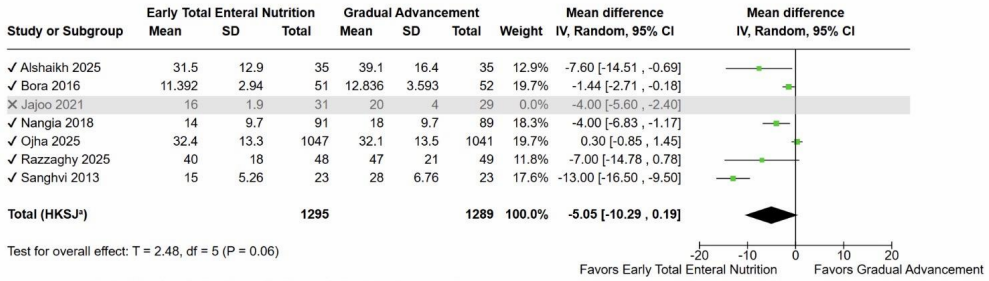
Test for overall effect: T = 2.88, df = 5 (P = 0.03)

Heterogeneity: Tau² (REML[b]) = 19.96; Chi² = 64.91, df = 5 (P < 0.00001); I² = 93%

Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.



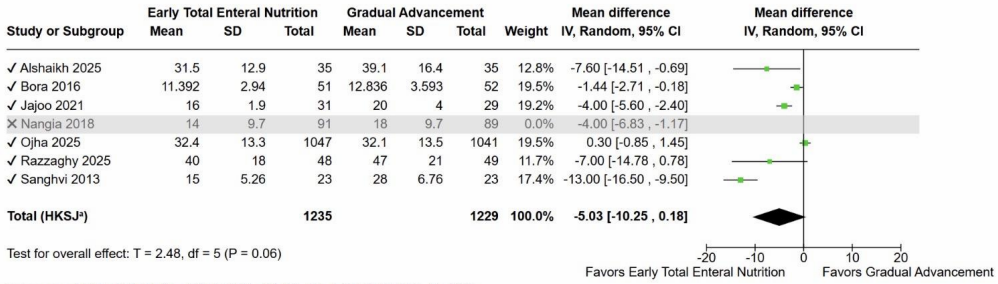
Test for overall effect: T = 2.48, df = 5 (P = 0.06)

Heterogeneity: Tau² (REML[b]) = 22.71; Chi² = 58.77, df = 5 (P < 0.00001); I² = 95%

Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.



Test for overall effect: T = 2.48, df = 5 (P = 0.06)

Heterogeneity: Tau² (REML[b]) = 22.47; Chi² = 64.06, df = 5 (P < 0.00001); I² = 96%

Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

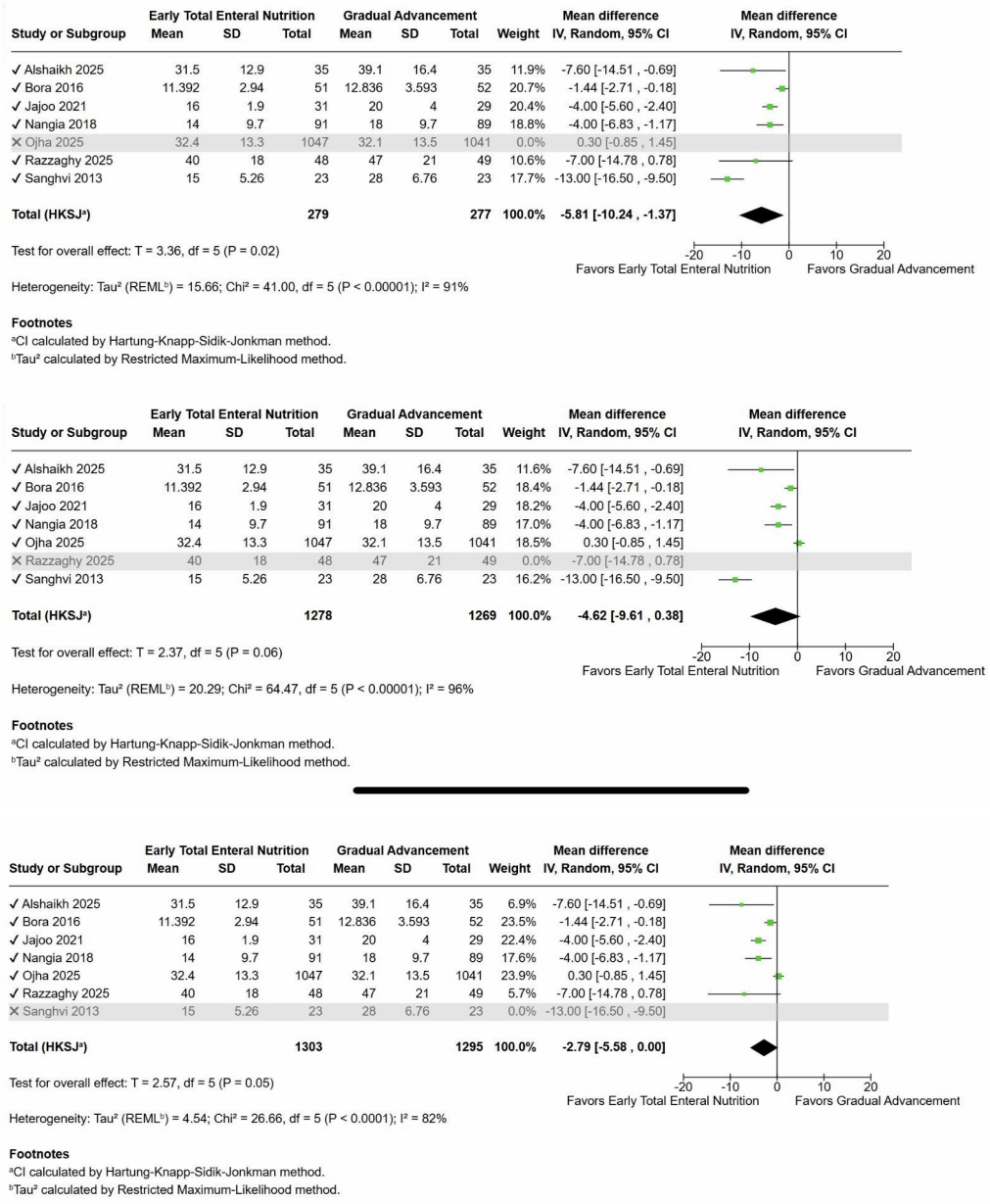
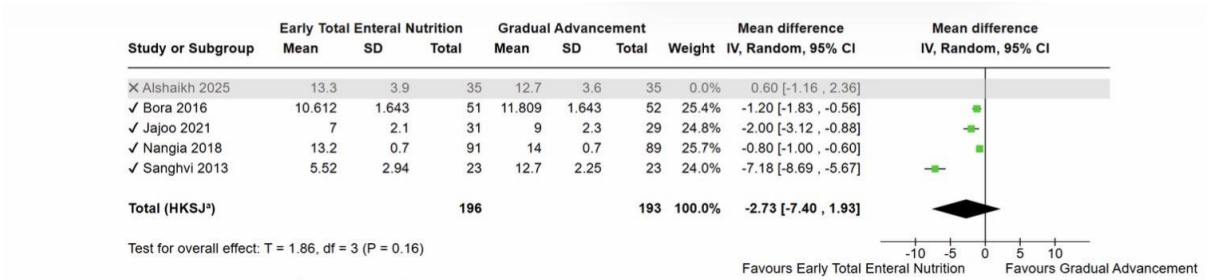


Figure S7 Leave-one-out sensitivity analysis for length at hospital



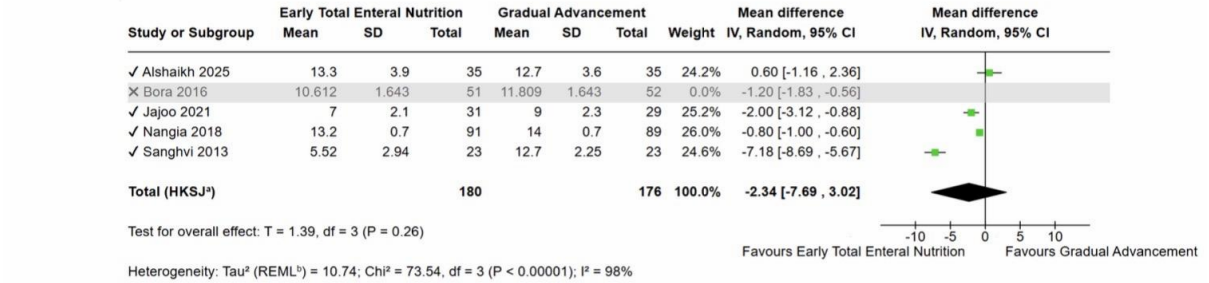
Test for overall effect: T = 1.86, df = 3 (P = 0.16)

Heterogeneity: Tau² (REML[b]) = 8.15; Chi² = 71.13, df = 3 (P < 0.00001); I² = 99%

Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.



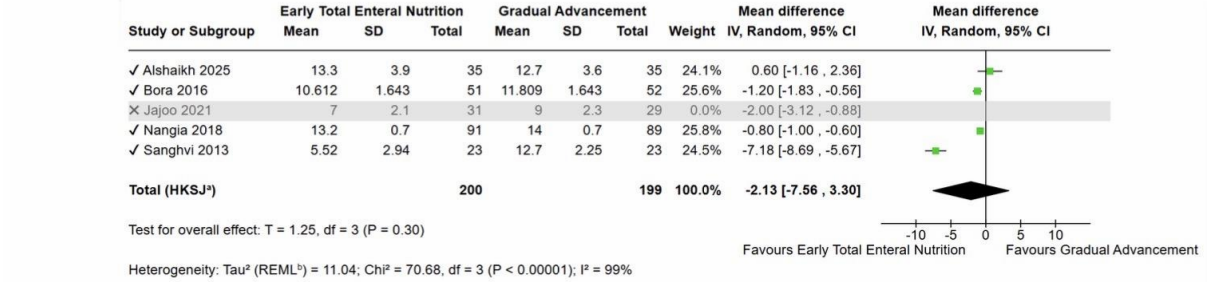
Test for overall effect: T = 1.39, df = 3 (P = 0.26)

Heterogeneity: Tau² (REML[b]) = 10.74; Chi² = 73.54, df = 3 (P < 0.00001); I² = 98%

Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.



Test for overall effect: T = 1.25, df = 3 (P = 0.30)

Heterogeneity: Tau² (REML[b]) = 11.04; Chi² = 70.68, df = 3 (P < 0.00001); I² = 99%

Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

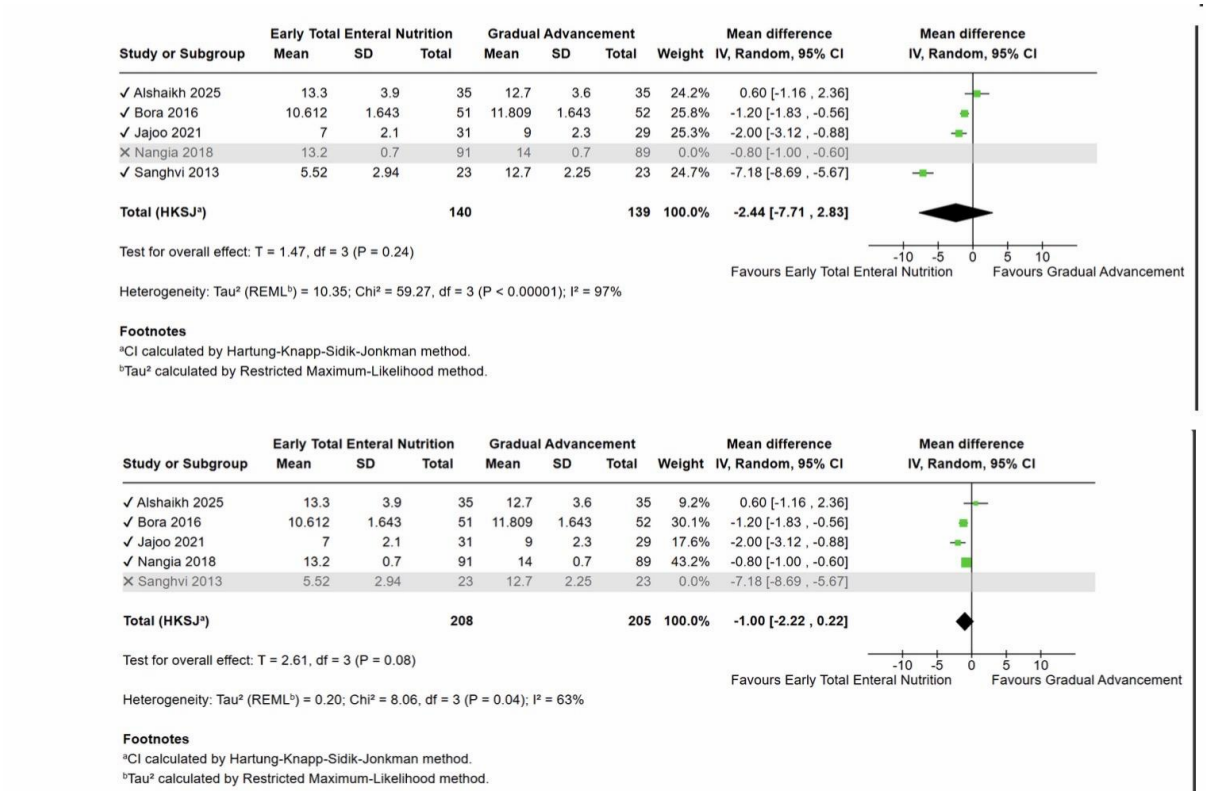


Figure S8 Leave-one-out sensitivity analysis for time to regain birth weight

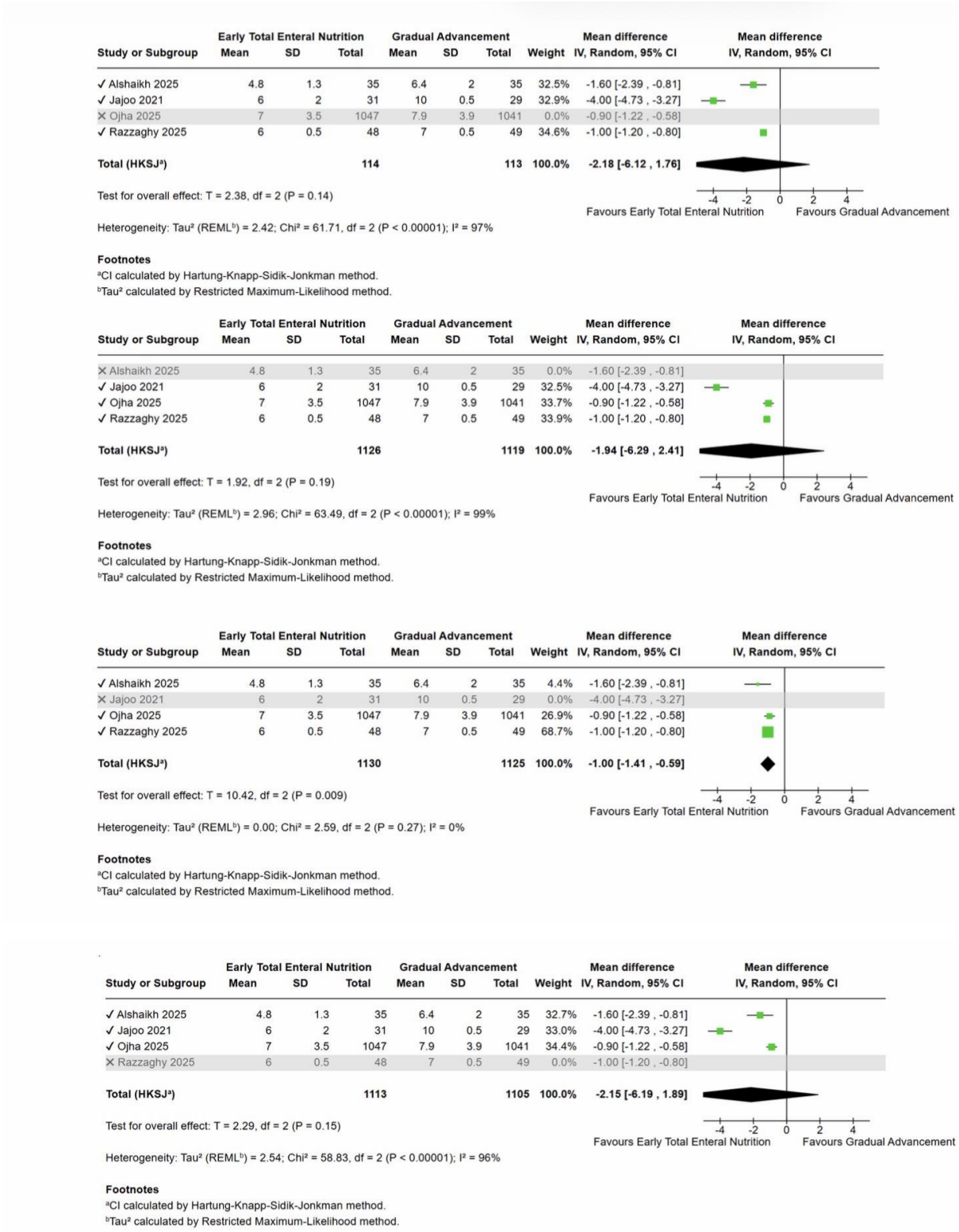


Figure S9 Leave-one-out sensitivity analysis for time to achieve enteral feed

Early Total Enteral Nutrition compared to Gradual Advancement for Preterm Infants

Patient or population: Preterm Infants
Setting:
Intervention: Early Total Enteral Nutrition
Comparison: Gradual Advancement

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Gradual Advancement	Risk difference with Early Total Enteral Nutrition
Necrotising enterocolitis	2511 (5 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 0.88** (0.39 to 1.98)	12 per 1.000	**1 fewer per 1.000** (from 7 fewer to 12 more)
Time to achieve enteral feed	2315 (4 RCTs)	⨁◯◯◯ Very low[a,b]	-		MD **1.85 days lower** (4.14 lower to 0.45 higher)
Feed intolerance	459 (5 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 0.82** (0.41 to 1.65)	215 per 1.000	**39 fewer per 1.000** (from 127 fewer to 140 more)
Sepsis	2444 (5 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 0.68** (0.29 to 1.58)	71 per 1.000	**23 fewer per 1.000** (from 51 fewer to 41 more)
Time to regain birth weight	459 (5 RCTs)	⨁◯◯◯ Very low[a,b]	-		MD **2.1 days lower** (5.75 lower to 1.56 higher)
Length at hospital	2644 (7 RCTs)	⨁◯◯◯ Very low[a,b]	-		MD **4.81 days lower** (9 lower to 0.61 lower)
Duration of IV fluid	2361 (4 RCTs)	⨁◯◯◯ Very low[a,b]	-		MD **3.19 days lower** (5.37 lower to 1.01 lower)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Wide confidence interval.
b. High heterogeneity

Figure S10 GRADE pro assessment