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Meta-analyses

Prebiotic supplementation in preterm neonates: Updated systematic review and meta-analysis of randomised controlled trials

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SUMMARY

Background & aims: Regular administration of prebiotic oligosaccharides promote beneficial gut flora in infants. We aimed to systematically review randomized controlled trials evaluating the safety and efficacy of prebiotic oligosaccharide supplementation in preterm infants ≤37 weeks of gestation.
Methods: Available studies from Medline, Embase, comparing formula milk supplemented with or without prebiotics, reporting on safety and the incidence of necrotising enterocolitis (NEC), late onset sepsis, feed tolerance, physical growth and various stool characteristics were eligible.
Results: 7 trials ($n = 417$) were included. Five trials ($n = 345$) reported on the incidence of NEC, 3 trials ($n = 295$) reported on the incidence of late onset sepsis. Meta-analysis revealed a pooled RR (95% CI) of 1.24 (0.56–2.72) for NEC, 0.81 (0.57–1.15), p 0.23 for the risk of late onset sepsis. 3 individual trials ($n = 295$) did not observe any improvement in time to enteral feeds post intervention. Meta-analysis indicated a statistically significant difference in the growth of bifidobacteria in the oligosaccharide group with a weighted mean difference of 0.53 (95% CI: 0.33, 0.73) $*10^6$ colonies/g, $p < 0.00001$. A reduction in stool viscosity and pH was also observed. None of the trials reported life threatening adverse effects.
Conclusions: Supplementation with prebiotic oligosaccharides was safe and did not result in decreased incidence of NEC, late onset sepsis and time to full enteral feeds but resulted in a significantly higher growth of beneficial microbes.

1. Introduction

Significance of gut flora in the gastrointestinal tracts of newborn infants is well understood.[1,2,3] Prebiotic oligosaccharides (prebiotic OS) are non-digestible food ingredients that selectively stimulate the growth of probiotic bacterial species in the colon, such as bifidobacteria and lactobacilli, which have the potential to improve host health. Human breast milk is the natural source of prebiotic OS. Various synthetic prebiotic OS such as short chain galacto oligosaccharides (GOS), long chain fructooligosaccharides (FOS), inulin, lactulose are available that mimic natural pre OS. Different prebiotic OS tend to offer different advantages. A combination of short chain and long chain pre OS has been thought to mimic natural human milk oligosaccharides the best. Regular administration of prebiotic OS has been shown to improve the gut flora and minimise the growth of pathogenic bacteria in preterm neonates.[4] Although prebiotic OS supplementation is considered safe, its clinical benefits in preterm infants (e.g. improving feed tolerance, preventing necrotising enterocolitis (NEC)) have not been evaluated properly.[5] The prebiotic summit in 2008 called for well designed clinical trials to advance further knowledge in this field.[6] Since the publication of our systematic review in 2009, more trials have been reported that assessed the clinical benefits of prebiotic OS in preterm infants.[7,8] These trials have demonstrated trend towards fewer episodes of late onset sepsis and a possible benefit towards promoting enteral feed tolerance in preterm infants.[7,8] A recent systematic review did not find any evidence that prebiotic supplementation improved weight, length, and head circumference in preterm infants.[9] Given the clinical importance of such findings, we aimed to update our previously published systematic review.[5]

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1.1. Primary objective

To systematically review randomised controlled trials assessing the safety and efficacy of prebiotic OS supplementation in reducing the risk of NEC and late onset sepsis, and facilitating feed tolerance and physical growth in preterm infants born less than 37 weeks of gestation.

1.2. Secondary objectives

Evaluate the effect of prebiotic OS supplementation on gut colonisation, physical characteristics of stool and gastrointestinal transit time in preterm infants.

2. Materials and methods

Guidelines from the Cochrane Neonatal Review group, PRISMA statement and the Centre for Reviews and Dissemination group were followed for conducting and reporting this systematic review and meta-analysis.[10,11] In order to be included in this review, the trials had to meet the following criteria:

2.1. Study design

Only randomised controlled trials and quasi-randomised trials published in any language were eligible for inclusion. Case series, retrospective studies, cross over trials, and uncontrolled trials were not eligible.

2.2. Participants

Trials in the preterm infants with gestation < 37 weeks at birth were eligible for inclusion. Trials were excluded if the post-conceptional age at randomisation was >40 weeks.

2.3. Interventions

Trials comparing formula milk supplemented with prebiotic OS vs placebo or unsupplemented formula milk were eligible for inclusion. Trials that supplemented breastfed infants with prebiotic OS were also eligible for inclusion. The prebiotic OS could be GOS, FOS, acidic oligosaccharide (AOS), inulin or lactulose. The supplementation should have continued for at least two weeks. Trials comparing combination of pre and probiotics vs controls were excluded. Trials in which composition of the intervention formula was different from that of controls (e.g, high quantity of beta palmitic acid, use of hydrolysed formula, etc.) were not eligible for inclusion.

2.4. Outcomes measures

Trials with at least one of the following outcome measures were included: incidence of NEC according to Bell stage, blood culture positive late onset sepsis, enteral feed tolerance, symptoms of intolerance to OS supplementation such as vomiting, diarrhoea, regurgitation, irritability and crying leading to cessation of supplementation or any other adverse outcome as reported by the authors. Other outcomes included stool colony count of bifidobacteria, lactobacilli and colonisation with enteric pathogenic bacteria, stool characteristics (e.g., pH, consistency, and frequency), age at full feeds, weight gain during hospital stay, death before discharge from the hospital, gastric or gastrointestinal transit time measurement.

2.5. Search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane library, Issue 2, 2012), Medline (1966 to July 2012), CINAHL (Cumulative Index of Nursing and allied Health Literature) EMBASE databases, and proceedings of the Pediatric Academic Society Meetings (published online from year 2007), and Pediatric Gastroenterology conferences (from year 2007) were searched in February and July 2012. Medline was searched using the following MeSH words: "Oligosaccharides" AND "Infant Formula" AND "Infant" OR "Infant, Very Low Birth Weight" OR "Infant, Low Birth Weight" OR "Infant, Extremely Low Birth Weight" OR "Infant, Premature" OR "Infant, Newborn" OR "Infant, Small for Gestational Age" OR "Infant, Premature" with limits of "Randomised Controlled Trial, Clinical trial". The search was repeated using the text word "prebiotic" instead of "Oligosaccharides." Text words, 'Inulin' and 'Lactulose' were used to identify additional studies. The reference lists of identified articles and key review articles were searched for additional studies. RS and SR searched the literature independently and assessed the eligibility of trials for inclusion in the review. Any differences were resolved by discussion with the third reviewer (SP).

2.6. Assessment of risk of bias

The methodological quality and the risk of bias of the included trials in terms of randomisation, blinding, allocation concealment, bias, internal validity was assessed separately by the reviewers RS and SR using the Cochrane methodology for systematic review of interventional studies.[10] In the event of disagreement, consensus was reached by discussion with the third reviewer (SP).

2.7. Data extraction

RS and SR independently extracted the data on a custom designed data collection form. Important data items included demographic characteristics, age at starting prebiotic OS, duration of supplementation, predefined outcome measures and adverse effects. Inconsistencies were resolved by discussion between all three reviewers. In the previous review, the authors of identified studies were contacted to improve the methodological quality of reporting and the results.[5] Since the newly added studies were assessed to be of good quality, a decision was made to use only the published data.

2.8. Statistical analysis

Meta-analysis was done using Review Manager 5.1 software from The Cochrane collaboration.[12] Weighted mean difference (WMD) and 95% confidence interval (CI) were calculated for continuous outcomes. Risk ratio was used for summary measure. Heterogeneity was estimated by the I squared statistic. A fixed effects model was used. The results were cross checked with the random effects model.

3. Results

3.1. Search results

Medline search using the previously described MeSH words and combinations revealed 180 studies. The study log and study selection process is presented in Fig. 1.

3.2. Methodological quality

The assessment of methodology and the risk of bias were performed using the Cochrane methodology for interventional trials.[10]