



ORIGINAL ARTICLE

Probiotic associations in the prevention of necrotising enterocolitis and the reduction of late-onset sepsis and neonatal mortality in preterm infants under 1500 g. A systematic review[☆]

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KEYWORDS

Very-low birth weight infants;
Necrotising enterocolitis;
Probiotics;
Premature infant;
Mortality;
Late-onset sepsis

Abstract

Introduction: Necrotising enterocolitis (NEC) is one of the most common and serious acquired bowel diseases a premature newborn can face. This meta-analysis was performed comparing different probiotic mixtures to ascertain their benefits as a routine tool for preventing necrotising enterocolitis and reducing late-onset sepsis and mortality in premature neonates of less than 1500 g.

Methods: A systematic review of randomised controlled trials, between January 1980 and March 2014, on MEDLINE, the Cochrane Central Register of Controlled Trials, together with EMBASE, was carried out. Studies with infants <1500 g or <34 weeks were selected, discarding those with Jadad scores lower than 4.

Results: 9 studies were selected for further investigation, pooling a total of 3521 newborns. Probiotics were found to reduce the NEC incidence (RR 0.39; 95% CI: 0.26–0.57) and mortality (RR 0.70; 95% CI: 0.52–0.93), with no difference to placebo regarding late-onset sepsis (RR 0.91; 95% CI: 0.78–1.06). Finally, when analysing the different strands, the use of a 2-probiotic combination (*Lactobacillus acidophilus* with *Bifidobacterium bifidum*) proved to be statistically significant in reducing all-cause mortality when compared to other probiotic combinations (RR 0.32; 95% CI: 0.15–0.66, NNT 20; 95% CI: 12–50).

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PALABRAS CLAVE

Neonatos de muy bajo peso;
Enterocolitis necrotizante;
Probióticos;
Prematuro;
Mortalidad;
Sepsis tardía

Conclusions: Probiotics are a beneficial tool in the prevention of NEC and mortality in preterm neonates. Moreover, the combination of 2 probiotics (*L. acidophilus* with *B. bifidum*) seems to produce the greatest benefits. However, due to the differences in probiotic components and administration, it would be wise to perform a randomised controlled trial comparing different probiotic mixtures.

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Asociaciones de probióticos para la prevención de la enterocolitis necrosante y la reducción de la sepsis tardía y la mortalidad neonatal en recién nacidos pretérmino de menos de 1500 g: Una revisión sistemática

Resumen

Introducción: Los recién nacidos pretérminos y de muy bajo peso presentan mayor riesgo de enterocolitis necrosante (NEC) dado que su colonización a nivel intestinal se produce más tardíamente y es diferente respecto a los recién nacidos a término, además de presentar con mayor frecuencia otros factores favorecedores como isquemia intestinal. Se cree que los probióticos pueden modificar la microbiota y la respuesta inmune de los recién nacidos, disminuyendo la incidencia de NEC.

Objetivo: Revisar los estudios realizados con diferentes probióticos y comparar diferentes combinaciones de éstos para ver si es beneficiosa su administración de forma rutinaria en recién nacidos pretérmino de menos de 1500 g para evitar la enterocolitis necrosante, reducir la sepsis tardía y la mortalidad.

Material y Métodos: Se llevó a cabo una revisión sistemática entre enero 1980 y marzo 2014, en MEDLINE, EMBASE y Cochrane Central Register of Controlled Trials. Se seleccionaron los estudios clínicos con recién nacidos prematuros de <1500 g y/o <34 semanas descartando aquellos con puntuaciones de Jadad menores de 4.

Resultados: Se seleccionaron 9 estudios, de 24 pre-seleccionados, con un total de 3521 recién nacidos. Se observó que los probióticos reducen la incidencia de NEC (RR 0,39; 95% CI: 0,26-0,57) y la mortalidad (RR 0,70; 95% CI: 0,52-0,93). No se detectaron diferencias significativas con el placebo en la disminución de sepsis tardía (RR 0,91; 95% CI: 0,78-1,96). Finalmente, cuando se analizan las distintas cepas, la combinación de 2 probióticos (*Lactobacillus acidophilus* con *Bifidobacterium bifidum*) demostró reducir la mortalidad de forma significativa comparada con otras combinaciones de probióticos (RR 0,32; 95% CI: 0,15-0,66, NNT 20; 95% CI: 12-50).

Conclusiones: Los probióticos son beneficiosos en cuanto a la prevención de NEC y reducen la mortalidad en pretérminos de menos de 1.500 g. Además, la combinación de dos probióticos (*Lactobacillus acidophilus* con *Bifidobacterium bifidum*) presenta mayor beneficio. Dada la diferencia de composición de probióticos son necesarios estudios aleatorizados comparando diferentes combinaciones de probióticos.

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Introduction

Necrotising enterocolitis (NEC) is one of the most common and serious acquired bowel diseases a newborn can face. Although it is not fully understood, the cause is suspected to be a combination of vascular necrosis, bacterial overgrowth and metabolic insults to the immature gut wall. It is believed that after toxic or ischaemic damage to the mural wall, and using the substrate proceeding from enteral feedings, there is an overgrowth of bacteria, especially those generating gases such as methane or hydrogen, producing intramural gas (pneumatosis intestinalis) leading to a mural necrosis, gut gangrene and, finally, intestinal

perforation with peritonitis. In recent years, there has also been a greater acceptance of the theory that the host's immune system also plays an important pathophysiological role in the development of NEC.¹

NEC predominantly affects premature infants, with 70–85% of cases of NEC occurring in very low birth weight infants (<1500 g) or infants younger than 32 weeks, whereas only 10–25% of cases are term infants or late preterm infants. The lower the gestational age, the higher the risk of NEC. Overall incidence of NEC has been reported as 7% in a study conducted by the National Institute of Child Health (NICHD) Neonatal Research Network (NRN) in a population of 11,072 very low birth weight infants (VLBW) for

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