Pediatr Surg Int (2018) 34:189–193
DOI 10.1007/s00383-017-4188-y

ORIGINAL ARTICLE

Probiotics for the prevention of Hirschsprung-associated enterocolitis: a systematic review and meta-analysis

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Accepted: 21 September 2017 / Published online: 5 October 2017

Abstract
Background/purpose Hirschsprung-associated enterocolitis (HAEC) is a life-threatening complication of Hirschsprung's disease. HAEC is reported to occur in 6–50% of patients preoperatively and in 2–35% postoperatively. The exact cause of HAEC is not fully understood, but disturbances of intestinal microbiota have recently been reported in patients with HAEC. In recent years, the administration of probiotics has been proposed to reduce the incidence of HAEC. We conducted a systematic review and meta-analysis to determine the effect of probiotics on postoperative HAEC.
Methods A systematic literature search for relevant articles was performed in four databases using the combinations of following terms "probiotics", "microbiota", "enterocolitis", "Lactobacillus", "Bifidobacterium", "Saccharomyces", "Streptococcus", and "Hirschsprung disease/Hirschsprung's disease" for studies published between 2002 and 2017. The relevant cohorts of the effect of probiotics in postoperative patients were systematically searched for clinical outcomes. Odds ratio (OR) or standard mean difference (SMD) with 95% confidence intervals (CI) were calculated using standardized statistical methodology.
Results The search strategy identified 1274 reports. Overall, five studies met defined inclusion criteria, reporting a total of 198 patients. Two studies were prospective multicenter randomized control trials. *Lactobacillus, Bifidobacterium, Streptococcus*, and *Enterococcus* were used as probiotics. The incidence of HAEC with/without probiotics was 22.6 and 30.5%, respectively, but this was not statistically different (OR 0.72; 95% CI 0.37–1.39; $P = 0.33$).
Conclusion This study shows that the administration of probiotics was not associated with a significant reduction in the risk of HAEC. Additional studies are required to understand more fully the role of microbiota and complex interactions that cause HAEC. With increasing knowledge of the role of microbiota in HAEC, we are likely to understand better the potential benefits of probiotics in this disease.

Keywords Probiotics · Hirschsprung's disease · Hirschsprung's-associated enterocolitis

Introduction

Probiotics are defined as live microorganisms, which when consumed in adequate amounts, which confer a health benefit on the host. In vitro studies suggest that probiotics potentially act favorably in the host through several different mechanisms. They have an antimicrobial effect through modifying the microflora, secreting antibacterial substances, competing with pathogens to prevent their adhesion to the intestinal epithelium, competing for nutrients necessary for pathogen survival, producing an antitoxin effect, and reversing some of the consequences of infection on the intestinal epithelium, such as secretory changes and neutrophil migration [1, 2]. Probiotics have been suggested to be efficacious in the prevention and treatment of viral diarrhea [3], necrotizing enterocolitis (NEC) [4], and pouchitis [5]. As well, probiotics can promote mucin production, which is

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deranged in Hirschsprung-associated enterocolitis (HAEC) [6]. It is well known that mucin layer blocks the direct attachment of commensal bacteria to the epithelial layer [6].

HAEC is a life-threatening complication of Hirschsprung's disease (HSCR). HAEC is reported to occur in 6–50% of patients preoperatively and in 2–35% postoperatively. The exact cause of HAEC is not fully understood. However, based on the previous knowledge of the beneficial effects of probiotics in inflammatory conditions of the gastrointestinal tract, some centres have advocated the prophylactic administration of probiotics after a pull-through procedure in patient with HSCR in anticipation that this will decrease the incidence of HAEC [7, 8]. We conducted a systematic review and meta-analysis to determine the effect of probiotics on postoperative HAEC.

Materials and methods

A systematic review and meta-analysis were conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic search of the literature was performed in the PubMed, Embase, Medline, and Cochrane Library electronic database for the keywords "probiotics", "microbiota", "enterocolitis", "Lactobacillus", "Bifidobacterium", "Saccharomyces", "Streptococcus", and "Hirschsprung disease/Hirschsprung's disease" for studies published between 2002 and 2017. Reference lists of relevant articles were manually searched for further cohorts. Duplicates were deleted. Resulting publications were reviewed in detail for epidemiology, operative treatment, morbidity, and clinical outcome. The relevant articles were reviewed by title, keywords, and abstract by the authors (H.N., T.L., and P.P.) and a full-text assessment of selected articles was performed.

Odds ratio (OR) or standard mean difference (SMD) with 95% confidence intervals (CI) was calculated using standardized statistical methodology.

Results

The initial search yielded a total of 1279 publications, of which 1274 were identified by electronic database searching and five from cross-referencing (Fig. 1). After removal of 512 duplicate listed articles, 767 titles, keywords, and

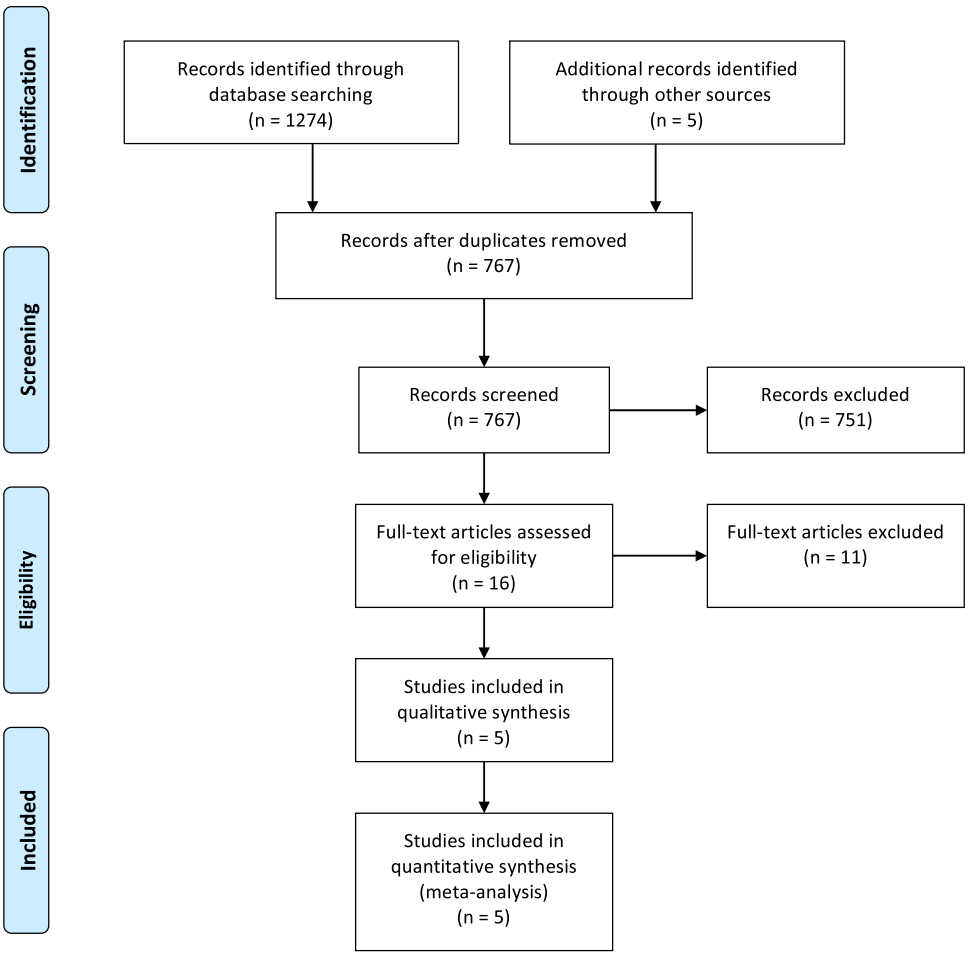

Fig. 1 This is an information flow diagram, demonstrating the process of selection and exclusion of articles from the literature search for the purposes of systematic review

abstracts were screened. Of these, 751 non-relevant studies were excluded. The remaining 16 publications were assessed in full text for eligibility and 11 articles were excluded, because they did not address any of the selection criteria. In total, data from five studies (published between 2002 and 2017) met defined inclusion criteria and were included in the cumulative analysis.

Five studies during the period 2011–2016 which met defined inclusion criteria reported a total of 198 patients [7–11] (Table 1). Two studies reported the type of HSCR; the incidence of long segment aganglionosis was not significantly different between probiotics group and placebo group. Two studies were prospective multicenter randomized control trials. *Lactobacillus, Bifidobacterium, Streptococcus*, and *Enterococcus* were used as probiotics. The incidence of HAEC with/without probiotics was 22.6 and 30.5%, respectively, but this was not statistically different (OR 0.72; 95% CI 0.37–1.39; $P = 0.33$) (Fig. 2).

Discussion

In recent years, a large number of randomized controlled trials have demonstrated a decrease in the incidence of NEC in premature infants following administration of probiotics, and therefore, probiotics have been proposed as an effective prophylaxis for NEC [4]. Based on this knowledge, administration of probiotics has been proposed to reduce the incidence of HAEC. However, the exact mechanism of action of probiotics therapy for HAEC is yet to be fully understood, and the benefits of probiotics for HAEC are not clear. Therefore, we conducted a systematic review and meta-analysis to determine the effect of probiotics prophylaxis on postoperative HAEC. The present meta-analysis revealed that administration of probiotics was not associated with a significant reduction in the risk of HAEC.

As pharmacological effects, it is thought that probiotics can directly supply the body's normal physiological bacteria, adjust the intestinal flora balance, inhibit and eliminate intestinal pathogens, reduce intestinal toxins, promote the body digesting nutrients, synthesize vitamins that organism required, and stimulate immunity [8]. Khan et al. [12] reported that probiotics potentially play a protective role in maintaining intestinal mucosal integrity through a number of different interaction, including alterations in mucosal cytokine expression, competing with intestinal pathogens for mucosal receptors, thereby increasing transepithelial resistance. Wang et al. [8] investigated the effect of oral probiotics in the patients with HSCR. Their result revealed that probiotics not only significantly decreased the incidence

Table 1 Study characteristics

Study	Country	Publish year	Probiotics (+)			Probiotics (−)			Probiotics
			Number	Number of HAEC	Incidence of HAEC (%)	Number	Number of HAEC	Incidence of HAEC (%)	
Demihri et al.	USA/Sweden	2016	7	3	43	11	6	55	–
El-Sawaf et al.	USA/Egypt	2013	28	10	36	32	7	22	*Lactobacillus Bifidobacterium Streptococcus*
Frykman et al.	USA/Sweden	2015	8	4	50	12	6	50	–
Wang et al.	China	2015	30	3	10	30	10	33	*Lactobacillus Bifidobacterium Enterococcus*
Yanbing et al.	China	2011	20	1	5	20	3	15	–

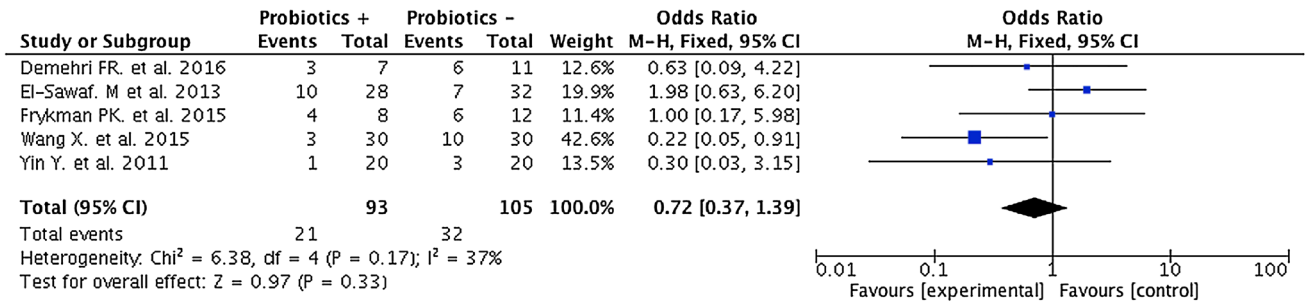

Fig. 2 Forest plots on incidence of Hirschsprung-associated enterocolitis

of HAEC but also decreased pro-inflammatory cytokines and increased anti-inflammatory cytokines. Shen et al. [13] reported markedly decreased *Lactobacilli* and *Bifidobacteria* in HAEC patients and speculated that this may result in a decrease in epithelial barrier function and be a predisposing factor in the development of HAEC. They suggested that treatment with probiotics may be beneficial in the prevention of HAEC [13].

Some case studies have reported sepsis associated with the use of probiotics [14]. In the present study, no studies reported side effects of probiotics. A recent review article summarized the side effects of probiotics [14]. There were some case reports that clearly documented occurrences of sepsis caused by the administered probiotic microbe. This risk is particularly relevant to premature infants given the immaturity of their intestinal barrier and increased risk of translocation of intestinal microbes into the lymphatic and/or systemic circulation. Similarly, in the patients with HSCR, intestinal barrier dysfunction has been proposed as one of the causes of HAEC [15, 16]. Among the probiotic products commonly administered to premature infants, there are reports of sepsis from *Saccharomyces boulardii* in one preterm infant and three term infants [17, 18], *Lactobacillus rhamnosus* GG in several premature infants and term infants many of whom had either congenital heart disease, gastroschisis, or short gut syndrome [19–24], and in a few infants receiving probiotic *Bifidobacteria* [25–27].

The limitations of this study include small number of articles, only two randomized control trials, and ununified antibiotics. Accordingly, additional randomized control studies are needed using unified antibiotics including comparing probiotic strains, doses, duration of administration, and the incidence of sepsis.

In conclusion, this study showed that administration of probiotics was ineffective in a significant reduction in the risk of HAEC. Additional studies are required to understand more fully the role of microbiota and complex interactions that cause HAEC. With increasing knowledge of the role of microbiota in HAEC, we are likely to understand better the potential benefits of probiotics in this disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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