World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i1.69

World J Gastroenterol 2010 January 7; 16(1): 69-75
ISSN 1007-9327 (print)

BRIEF ARTICLE

Systematic review of randomised controlled trials: Probiotics for functional constipation

Anna Chmielewska, Hania Szajewska

Anna Chmielewska, Hania Szajewska, Department of Paediatrics, The Medical University of Warsaw, 01-184 Warsaw, Dzialdowska 1, Poland
Author contributions: Szajewska H wrote the initial protocol of the review; Chmielewska A and Szajewska H were responsible for the literature search, study selection, methodological quality assessment, and data extraction; Szajewska H and Chmielewska A conducted the analyses and wrote the manuscript; Both authors contributed to the data interpretation; Szajewska H and Chmielewska A wrote the final report, which was approved by both authors; Szajewska H is the guarantor.
Supported by The Medical University of Warsaw, Poland
Correspondence to: Hania Szajewska, MD, Department of Paediatrics, The Medical University of Warsaw, 01-184 Warsaw, Dzialdowska 1, Poland. hania@ipgate.pl
Telephone: +48-22-4523309 Fax: +48-22-4523309
Received: September 23, 2009 Revised: October 26, 2009
Accepted: November 2, 2009
Published online: January 7, 2010

Abstract

AIM: To systematically evaluate and update evidence on the efficacy and safety of probiotic supplementation for the treatment of constipation.

METHODS: The MEDLINE, EMBASE, CINAHL, and Cochrane Library databases were searched in May 2009 for randomised controlled trials (RCTs) performed in paediatric or adult populations related to the study aim.

RESULTS: We included five RCTs with a total of 377 subjects (194 in the experimental group and 183 in the control group). The participants were adults (three RCTs, n = 266) and children (two RCTs, n = 111) with constipation. In adults, data suggests a favourable effect of treatment with *Bifidobacterium lactis* DN-173 010, *Lactobacillus casei* Shirota, and *Escherichia coli* Nissle 1917 on defecation frequency and stool consistency. In children, *L. casei rhamnosus* Lcr35, but not *L. rhamnosus* GG, showed a beneficial effect.

CONCLUSION: Until more data are available, we believe the use of probiotics for the treatment of constipation condition should be considered investigational.

Key words: Randomised controlled trials; Constipation; Probiotics; Adults; Children

Peer reviewer: Kristin A Verbeke, Professor, Pathophysiology, Section of Gastroenterology, Katholieke Universiteit Leuven, Herestraat 49, Leuven 3000, Belgium

Chmielewska A, Szajewska H. Systematic review of randomised controlled trials: Probiotics for functional constipation. *World J Gastroenterol* 2010; 16(1): 69-75 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i1/69.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i1.69

INTRODUCTION

Constipation is a common condition affecting children and adults[1,2]. In the vast majority of cases, no underlying organic cause is found and functional constipation is diagnosed[3,4]. The standard treatment consists of disimpaction and the administration of laxatives to achieve a normal bowel habit of passing a soft stool without pain. Even though traditional treatment is well established and safe, for many patients it does not provide satisfying improvement, prompting interest in other therapeutic strategies[5].

Currently, probiotics, defined as live microorganisms which when administered in adequate amounts confer a health benefit on the host[6], are increasingly being used in the management of constipation. Those most widely studied are organisms within the genera *Bifidobacterium*

and *Lactobacillus*. There are several reasons why probiotics might have therapeutic potential for the treatment of constipation. Firstly, there are data demonstrating differences in the intestinal microbiota between healthy individuals and patients with chronic constipation[7,8]. The key features are an increased number of clostridia and bifidobacteria, with different species of clostridia and enterobacteriaceae being frequently isolated. A number of key questions remain to be answered, principally, what is the origin of this dysbiosis? Is dysbiosis a secondary manifestation of constipation, or is it a factor contributing to constipation? Secondly, studies involving the administration of *B. lactis* DN-173 010 have shown improved colonic transit times, both in a healthy population[9] and in constipated patients[10]. Finally, probiotics lower the pH in the colon. This reduction in pH is due to the bacterial production of short-chain fatty acids (butyric acid, propionic acid, and lactic acid). A lower pH enhances peristalsis in the colon[8] and, subsequently, might decrease the colonic transit time.

In view of the uncertainty regarding the use of probiotics for the treatment of constipation, we decided to systematically review and update data from randomised controlled trials (RCTs) on the efficacy and safety of using probiotics for the treatment of constipation in both paediatric and adult populations. If the probiotics were effective, another aim was to determine what strain(s) of probiotic microorganisms is the most effective.

MATERIALS AND METHODS

The guidelines from the Cochrane Collaboration for undertaking and reporting the results of this systematic review were followed[11]. Briefly, we searched three electronic bibliographic databases (MEDLINE, EMBASE, and CINAHL) and the Cochrane Library. Every database was searched from inception to May 2009. Additionally, the reference lists from identified studies and key review articles assessing the effects of probiotics on the treatment of constipation were searched. While no language restrictions were applied, in practice the search was restricted to English-language papers, papers written in languages known to the reviewers, or those with English-language abstracts. The review was restricted to RCTs only carried out in paediatric or adult populations. Participants in the experimental groups received any well-defined probiotic at any dosage regimen for at least several days; those in the control group received placebo or no intervention. The search strategy included the use of a validated filter for identifying RCTs, which was combined with a topic-specific search strategy. In brief, the search terms were: *constipation* AND *probiotic*, Lactobacillus, L. GG, L. acidophilus, L. rhamnosus, L. plantarum, L. casei, L. gasseri, L. reuteri, L. lactis, Bifidobacterium, B. breve, B. longum, B. infantis, B. adolescentis, B. lactis, Bacillus, Clostridium butyricum, Streptococcus thermophilus, Escherichia coli, Propionibacterium freundendsreichii, Enterococcus SF68, Enterococcus faecalis, Saccharomyces boulardi,* and *VSL#3*. The primary clinical outcome measure was treatment success (as defined by the investigators). In addition, a priori it was decided to extract other data reported by the investigators if clinically relevant to the current review and/or adverse effects. All of the published studies that met our eligibility criteria were assessed for methodological quality, with the following strategies associated with good-quality studies: adequate generation of allocation sequences; concealment of allocation; blinding of investigators, participants, outcome assessors, and data analysts; intention-to-treat analysis (yes or no); and comprehensive follow-up ($\geqslant$ 80%).

Data extraction was performed using standard data-extraction forms. For dichotomous outcomes, the total number of participants and the number of participants who experienced the event were extracted. For continuous outcomes, the total number of participants and the means and standard deviations were extracted. If feasible, the data were entered into Review Manager (RevMan) (Computer program. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2007) for analysis.

Statistical methods

As the studies we identified were not sufficiently similar and of sufficient quality we did not perform a meta-analysis. The binary measure for individual studies is reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (95% CI). The mean difference (MD) between the treatment and control groups was selected to represent the difference in continuous outcomes (with 95% CI).

A priori defined subgroup analyses were planned based on factors that could potentially influence the magnitude of the treatment effect, such as the probiotic strain or study population (children, adults); however, these analyses were not performed due to the limited data available.

RESULTS

By means of our systematic search, we identified six trials[12-17]. One was a protocol of an ongoing study[15], so it was not included. Thus, eventually five trials, including a total of 377 subjects (194 in the experimental group and 183 in the control group), met our predefined inclusion criteria. The characteristics of the included studies are presented in Table 1. The list of excluded trials (n = 22) is available upon request. The most usual reason for exclusion of a study was that the study was not randomised, the study was carried out in healthy volunteers, or the intervention was treatment with a symbiotic, not a probiotic alone. In addition, some studies were published in Japanese with no English abstract, and thus, were not accessible to the reviewers, even for initial screening.

All of the trials were full peer-reviewed publications.

Table 1 Characteristics of included trials

Study ID	Probiotic	Design	Allocation concealment/ Blinding/Intention-to-treat analysis/Description of withdrawals or dropouts	Exp/cont (age, yr)	Definition of constipation	Duration of intervention	Intervention (daily dose)	Placebo
Studies in adults								
Mollenbrink *et al*[13] 1994 (Germany)	*E. coli* Nissle 1917	RCT, crossover	Unclear/Yes/No/Yes	35/35 (18-60)	< 2 BM per week	4 + 4 wk	25×10^9 CFU	Placebo
Koebnick *et al*[12] 2003 (Germany)	*L. casei* Shirota	RCT, parallel	Unclear/Yes/Yes/Yes	35/35 (18-70)	Not provided	4 wk	6.5×10^9 CFU, probiotic beverage	Placebo
Yang *et al*[14] 2008 (China)	*B. lactis* DN-173 010	RCT, parallel	Unclear/No/Yes/Yes	63/63 (25-65, only women)	< 3 BM per week; increased stool hardness; non-organic constipation and habitual constipation	2 wk	Fermented milk containing 1.25 $\times 10^{10}$ CFU of probiotic plus yoghurt strains	Placebo (acidified milk without any ferments or probiotics)
Studies in children								
Banaszkiewicz *et al*[17] 2005 (Poland)	*L. rhamnosus* GG	RCT, parallel (computer-generated randomisation list)	Yes/Yes/Yes/Yes	43/41 (2-16)	< 3 BM per week during 14 days for at least 12 wk	12 wk	Lactulose plus LGG 2×10^9 CFU	Lactulose plus placebo
Bu *et al*[16] 2007 (Taiwan)	*L. casei* rhamnosus Lcr35	RCT, parallel (computer-generated randomisation list)	Yes/Yes/Yes/Yes	18/9 (< 10)	< 3 BM per week for > 2 mo plus at least one of the criteria: anal fissures with bleeding due to constipation, faecal soiling, or passage of large and hard stool	4 wk	8×10^8 CFU	Placebo (starch)

RCT: Randomised controlled trials; CFU: Colony-forming units; BM: Bowel movements.

Four of the included studies were RCTs with a parallel design, and the remaining included RCT had a crossover design. All were placebo-controlled trials. The participants were adults (three RCTs, $n = 266$) and children (two RCTs, $n = 111$) with constipation defined as stated in Table 2. The following different probiotic strains were tested: *Bifidobacterium lactis* DN-173 010, *E. coli* Nissle 1917, *Lactobacillus casei rhamnosus* Lcr35, *L. casei* Shirota, and *L. rhamnosus* GG. One RCT assessed the effectiveness of using *L. rhamnosus* GG as an adjunct to lactulose therapy compared with treatment with lactulose alone[17]. The durations of the interventions in the parallel-design studies were two weeks in one study, four weeks in two studies, and 12 wk in one study. The duration of the intervention in the crossover design study was eight weeks. The doses of the probiotic used ranged from 8×10^8 to 25×10^9 colony-forming units (CFU)/d.

The methodological quality of the trials varied. While all were randomised trials, the randomisation method was described and adequate in only two RCTs[16,17]. Except for one study[14], double blinding was applied in the remaining RCTs. An adequate description of the intention-to-treat analysis was provided in all but one study[13]. The withdrawals and dropouts were described adequately in all of the studies, and all included an adequate number (i.e. $\geqslant 80\%$) of participants in the final analysis.

Study description

RCTs in adults: The study by Mollenbrink and Bruckschen[13] was a single-centre, randomised, double-blind, crossover trial that investigated the efficacy of treating 70 constipated patients with *E. coli* Nissle 1917 or placebo. After four weeks of treatment, there was a significant difference in the mean number of stools per week in the *E. coli* group compared with the placebo group (4.9 ± 1.5 *vs* 2.6 ± 1.0, respectively, MD 2.3 stools per week, 95% CI 1.7 to 2.9), which also remained significant at eight weeks (6 ± 1.3 *vs* 1.9 ± 1.5, respectively, MD 4.1, 95% CI 3.2 to 5). This study also revealed a significant difference between the probiotic and the control group in the incidence of hard stools (2/34 *vs* 16/30, respectively, RR 0.1, 95% CI 0.03 to 0.4). Both the effectiveness and tolerance of the treatment, as assessed both by a physician and the patients, were significantly better in

Table 2 The summary of study outcomes

Study ID	Probiotic	Outcomes
Studies in adults		
Mollenbrink *et al*[13] 1994 (Germany)	*E. coli* Nissle 1917[1]	Number of stools per week [week 4: 4.9 ± 1.5 *vs* 2.6 ± 1.0, MD 2.3 (95% CI 1.7 to 2.9); week 8: MD 4.1 (95% CI 3.2 to 5)] Hard stools [2/34 *vs* 16/30, RR 0.1 (95% CI 0.03 to 0.4) ($P < 0.001$)] Effectiveness of a probiotic compared to placebo assessed by physicians: 55.9% *vs* 6.7% Effectiveness of a probiotic compared to placebo assessed by patients: 52.9% *vs* 6.7% ($P < 0.001$) Tolerance of a probiotic compared to placebo assessed by physicians: 58.85% *vs* 26.7% ($P = 0.01$) Tolerance of a probiotic compared to placebo assessed by patients: 50% *vs* 26.7% ($P = 0.03$)
Koebnick *et al*[12] 2003 (Germany)	*L. casei* Shirota[2]	Occurrence of moderate and severe constipation ($P < 0.001$) Degree of constipation ($P = 0.003$) Defecation frequency ($P = 0.004$) Occurrence of hard stools ($P < 0.001$) Degree of stool consistency ($P < 0.001$) Occurrence of flatulence (NS) Degree of flatulence (NS) Occurrence of bloating (NS) Degree of bloating (NS)
Yang *et al*[14] 2008 (China)	*B. lactis* DN-173 010[1]	Stool frequency (*n*/wk) [week 1: 3.5 ± 1.5 *vs* 2.5 ± 0.9, MD 1 (95% CI 0.6 to 1.4); week 2: 4.1 ± 1.7 *vs* 2.6 ± 1.0; MD 1.5 (95% CI 0.7 to 1.6)] Defection condition scores [week 1: 1.1 ± 0.9 *vs* 1.6 ± 1.1, MD -0.5 (95% CI -0.85 to -0.18); week 2: 0.8 ± 1.0 *vs* 1.6 ± 1.1; MD -0.8 (95% CI -1.14 to -0.44)] Grade Ⅰ (0 points)-normal defecation Grade Ⅱ (1 point)-only bearing down and uncomfortable sensation Grade Ⅲ (2 points)-obvious bearing down and uncomfortable sensation, or frequent defecation with difficult and little defecation, seldom abdominal pain or anal burning sensation Grade Ⅳ (3 points)-often abdominal pain or anal burning sensation to influence defecation Stool consistency scores (according to classification method of Bristol) [week 1: 1.0 ± 0.8 *vs* 1.4 ± 1.0, MD -0.4 (95% CI -0.73 to -0.12); week 2: 0.6 ± 0.8 *vs* 1.3 ± 1.0, MD -0.7 (95% CI -1 to -0.4)] Grade Ⅰ (0 points)-like sausage or snake, smooth and soft; like sausage, with fissure on the surface Grade Ⅱ (1 point)-sausage-shaped, with lumps; noncohesive lumps, with coarse edges Grade Ⅲ (2 points)-separating hard lumps, like fruit kernel (difficult discharge)
Studies in children		
Banaszkiewicz *et al*[17] 2005 (Poland)	*L. rhamnosus* GG[2]	Treatment success (≥ 3 spontaneous BMs per week with no episodes of faecal soiling) (NS) Number of BMs per week (NS) Number of episodes of faecal soling per week (NS) Straining at defecation frequency per week (NS)
Bu *et al*[16] 2007 (Taiwan)	*L. casei* rhamnosus Lcr35[1]	Treatment success (≥ 3 spontaneous BMs per week with no episodes of faecal soiling in the fourth week) (14/18 *vs* 1/9, RR 7, 95% CI 1.1 to 45; $P = 0.01$) Defecation frequency (times/d) (0.57 ± 0.17 *vs* 0.37 ± 0.1; MD 0.2, 95% CI 0.1 to 0.3)($P = 0.03$) Hard stool (%) (22.4 ± 14.7 *vs* 75.5 ± 6.1; MD -53% (95% CI -63 to -43) (($P = 0.01$) Abdominal pain (times) (1.9 ± 1.6 *vs* 6.7 ± 3.3; MD -4.8, 95% CI -6.6 to -3) ($P = 0.03$) Use of glycerin enema (times) (1.6 ± 1.9 *vs* 4.0 ± 2.1; MD -2.4, 95% CI -4 to -0.8) ($P = 0.04$) Use of lactulose (times) (4.4 ± 3.6 *vs* 6.2 ± 3.8; MD -1.8, 95% CI -4.7 to 1.1) ($P = 0.66$) Faecal soiling (times) (2.1 ± 3.8 *vs* 2.7 ± 1.4, MD -0.6 (95% CI -3.2 to 2) ($P = 0.95$) Change of appetite (0.7 ± 0.8 *vs* 0.7 ± 0.6; MD 0, 95% CI -0.6 to 0.6) ($P = 0.81$)

[1]Mean values are presented for the experimental group and control group, respectively; [2]Comparisons of experimental and control group. NS: Not significant.

those in the *E. coli* group. The authors concluded that *E. coli* Nissle 1917 is successful in the therapy of idiopathic chronic constipation.

The study by Koebnick *et al*[12] was a single-centre, double-blind, placebo-controlled, randomised trial involving 70 patients with symptoms of chronic constipation. All of the patients received either a probiotic beverage containing *L. casei* Shirota or placebo for four weeks. Patients completed a questionnaire related to their gastrointestinal symptoms, well-being, and stool habits, and underwent a medical examination weekly. The severity of constipation, flatulence, and bloating was divided into four categories (severe, moderately severe, mild, and no symptoms). Compared to the placebo group, those randomised to the *L. casei* Shirota group experienced a significant improvement in the self-reported severity of constipation and stool consistency. That is, they experienced significant reductions in the occurrence of moderate and severe constipation ($P < 0.001$), the degree of constipation ($P = 0.003$), and the occurrence of hard stools ($P < 0.001$), and increased their defecation frequency ($P = 0.004$). However, the occurrence and degree of flatulence or bloating sensation did not significantly differ between the groups.

In the most recent study, Yang *et al*[14] administered a fermented milk product containing *B. lactis* DN-173 010 and some yoghurt strains (*S. thermophilus* and *L. bulgaricus* (1.2×10^9 CFU/pot 100 g) (experimental group) or an acidified milk containing non-living bacteria but no *B. lactis* DN-173 010 or yoghurt strains (control group) for two weeks to constipated women. Comparison of the experi-

mental group with the control group revealed a significantly higher stool frequency after one week of product administration (3.5 ± 1.5 *vs* 2.5 ± 0.9, respectively, MD 1.0 stool per week, 95% CI 0.6 to 1.4) and at two weeks (4.1 ± 1.7 *vs* 2.6 ± 1.0, respectively, MD 1.5 stool per week, 95% CI 0.7 to 1.6). The extent of defecation difficulty was assessed as 0-3 point defecation condition scores. In brief, 0 points indicates normal defecation, while 3 points indicates often abdominal pain or anal burning sensation to influence defecation. (Table 2 for complete categorisation of defecation condition scores). Both at one and two weeks after product consumption, there was a significant improvement in the defecation condition scores in the experimental group compared with the control group: 1.1 ± 0.9 *vs* 1.6 ± 1.1, respectively (MD -0.5, 95% CI -0.85 to -0.18) at 1 wk and 0.8 ± 1.0 *vs* 1.6 ± 1.1, respectively (MD -0.79, 95% CI -1.14 to -0.44) at 2 wk. The stool consistency score was determined according to the Bristol Stool Scale. In brief, 0 points indicates stools like a sausage or a snake, smooth and soft, while 2 points indicates separating hard lumps, like fruit kernel (difficult discharge) (Table 2). The stool consistency scores were significantly improved in the *B. lactis* DN-173 010 group compared to the control group at 1 wk (1.0 ± 0.8 *vs* 1.4 ± 1.0, respectively, MD -0.4, 95% CI -0.73 to -0.12) and at 2 wk (0.6 ± 0.8 *vs* 1.3 ± 1.0, respectively, MD -0.7, 95% CI -1 to -0.4). There were no significant differences between groups in food intake and safety parameters. The researchers concluded that the administration of a fermented milk product containing *B. lactis* DN-173 010 has a beneficial effect on stool frequency, defecation conditions, and stool consistency in adult women with constipation.

RCTs in children: Only two RCTs have addressed the use of probiotics in the treatment of constipation in children. In the study by *Banaszkiewicz* and *Szajewska*[17], 84 children (aged: 2-16 years) with constipation (< 3 spontaneous bowel movements per week for at least 12 wk) were enrolled in a double-blind, randomised, placebo-controlled trial in which they received 1 mL/kg per day of 70% lactulose plus 10^9 CFU of *L. rhamnosus* GG (experimental group, n = 43) or a lactulose-containing placebo (control group, n = 41) orally twice daily for 12 wk. The primary outcome measure was treatment success; all analyses were performed on an intention-to-treat basis. Treatment success was defined as ⩾ 3 spontaneous bowel movements per week with no episodes of faecal soiling. Treatment success was similar in the control and experimental groups at 12 wk [28/41 (68%) *vs* 31/43 (72%), respectively; P = 0.7] and at 24 wk [27/41 (65%) *vs* 27/43 (64%), respectively; P = 1.0]. The groups also did not differ in their mean number of spontaneous bowel movements per week or episodes of faecal soiling per week at four, eight, and 12 wk. Adverse events and overall tolerance did not differ between groups. It was concluded that *L. rhamnosus* GG, as dosed in this study, was not an effective adjunct to lactulose in treating constipation in children.

The study by Bu *et al*[16] evaluated the effect of treating children with chronic constipation with *L. casei rhamnosus* Lcr35 compared to magnesium oxide (MgO) or placebo; however, only the latter comparison is valid for this systematic review. For those treated with the probiotic (n = 18) compared with placebo (n = 9), the trial showed an increase in the treatment success defined as ⩾ 3 spontaneous defecations per week with no episodes of faecal soiling (14/18 *vs* 1/9, respectively, RR 7, 95% CI 1.1 to 45), an increase in the defecation frequency (times/d) (0.57 ± 0.17 *vs* 0.37 ± 0.10, respectively, MD 0.2, 95% CI 0.1 to 0.3), a reduction in abdominal pain (frequency) (1.9 ± 1.6 *vs* 6.7 ± 3.3, respectively, MD -4.8, 95% CI -6.6 to -3), a reduction in the use of glycerin enemas during the four weeks of therapy (frequency) (1.6 ± 1.9 *vs* 4.0 ± 2.1, respectively, MD -2.4, 95% CI -4 to -0.8), and a decrease in the percentage of hard stools in the total number of defecations (22.4 ± 14.7 *vs* 75.5 ± 6.1, respectively, MD -53%, 95% CI -63 to -43). However, there was no difference between groups in the use of lactulose or the number of episodes of faecal soiling. No change in appetite was observed. However, the sample size was too small to draw any meaningful conclusion.

Adverse events

The probiotics were well tolerated, and no adverse events associated with this supplementation were reported in any of the trials.

DISCUSSION

Principal findings

The objective of this review was to provide some resolution to the uncertainty regarding the use of probiotics for the treatment of functional constipation in paediatric and adult populations. The main finding of the review is that there is very limited evidence available from controlled trials to evaluate with certainty the effect of probiotic administration on constipation. Data published to date suggest that adults with constipation might benefit from ingestion of *B. lactis* DN-173 010, *L. casei* Shirota, and *E. coli* Nissle 1917, which were shown to increase defecation frequency and improve stool consistency. However, in some cases, even if there was a significant difference in results, their clinical relevance is unclear. For example, compared with placebo, *B. lactis* DN-173 010 increased only by one the number of stools per week. In children, the administration of *L. rhamnosus* GG was not effective, while the administration of *L. casei rhamnosus* Lcr35 augmented the number of stools and reduced the number of hard stools. Again, although the results were statistically significant, the overall effects were clinically modest. All of the conclusions are based on single studies, some of which had a very small number of participants and methodological limitations; thus, the conclusions should be interpreted with great caution. Repeat studies with the probiotic strains that have been proven effective are needed. A paucity of data did not allow us to con-

clude whether any particular probiotic is more effective than another.

Previous reports

Previously, one systematic review[18], co-authored by one of the authors of the current review, aimed at determining the effect of probiotics on constipation was performed. This systematic review, published in 2005 (search date: January 2004), identified two RCTs with a total of 140 adult participants. It was concluded that the administration of two probiotic strains (*E. coli* Nissle 1917, *L. casei* Shirota) significantly improved stool frequency and consistency, with no difference in the degree of bloating or flatulence; no adverse effects were reported. Our updated results include results from more RCTs, thus, more precisely define the effects of using probiotics for the treatment of constipation.

Evidence from non-RCTs suggests that at least some probiotics may be effective. For example, in children with constipation defined according to the Rome Ⅲ criteria, the administration of *Bifidobacteria (B. bifidum, B. infantis,* and *B. longum)* and *Lactobacilli (L. casei, L. plantarum,* and *L. rhamnosus)* to 20 children aged 4-16 years resulted in an increased frequency of bowel movements, a decreased number of faecal incontinence episodes, and reduced abdominal pain, although there was no change in stool consistency[19]. In adults, preliminary data from a non-RCT revealed that the administration of *L. rhamnosus* and *Propionibacterium freudenreichii* resulted in a small, but significant, increase in defecation frequency[20]. However, this result was only true if the probiotics were administered together and not if only a single strain was given.

Mechanism of action

Mechanisms by which probiotics might work in the treatment of constipation have been briefly discussed in the Introduction section. Clearly, they are not well understood. Perhaps the best mechanism documented is the mechanism by which *B. animalis* DN-173 010 exerts its effects. In healthy subjects, several RCTs have evaluated the effect of *B. animalis* DN-173010 on colonic transit times. One double-blind RCT conducted in 72 healthy adults (aged 21-42 years) used radio-opaque pellets to measure colonic transit times. This study revealed a statistically significant reduction in the total colonic transit time of 21% (men: $P < 0.03$, women: $P < 0.05$) and a reduction in the sigmoid transit time of 39% ($P = 0.02$), particularly in women, with probiotic treatment. However, the beneficial effect was limited to the subjects who received living *B. animalis* DN-173 010 and was not observed in those who received heat-treated *B. animalis* DN-173 010[21]. Another double-blind RCT performed in 36 healthy women (aged 18-45 years) revealed significantly shorter total colonic and sigmoid colonic transit times ($P < 0.05$) following ingestion of 375 g/d of a fermented milk containing yoghurt cultures plus *B. animalis* DN-173 010 for 10 d, compared with the transit times observed with ingestion of the control probiotic-free product[22]. Two further non-blinded RCTs were carried out in healthy elderly subjects who were divided into groups according to their different baseline colonic transit times. Both studies demonstrated a reduction in transit times in all of the groups compared with baseline with consumption of fermented milk containing *B. animalis* DN-173 010[23,24]. Further studies are needed to confirm these findings.

Strengths and limitations

The advantage of any systematic review is the low risk of subjective data selection. Study searches, assessment, and data synthesis were all based on predefined criteria and were performed with the use of well-established repetitive tools by two reviewers independently. Nevertheless, our analysis has some limitations. First, we cannot fully exclude publication bias, i.e. publication or non-publication of data depending on the results, with negative findings being less likely to be published irrespective of the methodological quality. As studies involving the administration of probiotics are often supported by the manufacturers, the possibility remains that negative results remain unpublished. No sufficiently effective strategy of identifying such studies has been developed. Second, even though no language limitation was imposed, in practice it was not feasible to assess data from reports written in Japanese. Third, any systematic review is only as good as the constituent studies. Only some of the trials included in our analysis seemed methodologically sound. Potential limitations included unclear or inadequate allocation concealment, no intention-to-treat analysis, and no blinding. Fourth, some trials included a small sample size. Finally, the effects of probiotics are strain specific as well as population specific. While a systematic review or a meta-analysis on probiotics does provide valid information, caution should be exercised in not over interpreting the results of a meta-analysis, particularly when all probiotics have been evaluated together.

Safety issues

In general, the safety profile of probiotics seems to be good. In the included trials, no adverse effects were noted. The safety issue is important, as based on the available literature there is concern that the use of probiotics in at-risk populations may result in harmful events. Most complications have occurred in immunocompromised subjects or in patients with other life-threatening illnesses, who were managed in intensive care units and treated with probiotics.

In summary, this systematic review demonstrates that the data published to date do not yet provide sufficient scientific evidence to support a general recommendation about the use of probiotics in the treatment of functional constipation. Until such data are available, we believe that the use of probiotics for this condition should be considered investigational. Also, we believe that our demonstration of clinical uncertainty about this issue is

an important finding. As pointed out by Alderson and Roberts[25], clinical uncertainty is a prerequisite for the large-scale RCTs needed to evaluate the influence of such interventions; it also helps to clarify available treatment options and stimulate new and better research.

COMMENTS

Background

Probiotics are increasingly being used in pediatric population. However, there is still uncertainty regarding the use of probiotics for the treatment of constipation.

Research frontiers

Until more data are available, the use of probiotics for the treatment of constipation condition should be considered investigational. The large-scale RCTs are needed to evaluate the effect of specific probiotic strain(s) for the treatment of constipation.

Innovations and breakthroughs

The updated results include results from more RCTs; thus, more precisely define the effects of using probiotics for the treatment of constipation.

Applications

Until such data are available, the use of probiotics for this condition should be considered investigational.

Peer review

This manuscript describes a systematic review of randomised controlled trials that evaluated the efficiency of probiotics in the treatment of functional constipation.

REFERENCES

1 **van den Berg MM**, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. *Am J Gastroenterol* 2006; **101**: 2401-2409
2 **Higgins PD**, Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol* 2004; **99**: 750-759
3 **Rasquin A**, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, Walker LS. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2006; **130**: 1527-1537
4 **www.romecriteria.org/pdfs/AdultFunctGIQ.pdf**
5 **Bongers ME**, Benninga MA, Maurice-Stam H, Grootenhuis MA. Health-related quality of life in young adults with symptoms of constipation continuing from childhood into adulthood. *Health Qual Life Outcomes* 2009; **7**: 20
6 Joint FAO/WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food. London, Ontario, Canada, April 30 and May 1, 2002
7 **Zoppi G**, Cinquetti M, Luciano A, Benini A, Muner A, B ertazzoni Minelli E. The intestinal ecosystem in chronic functional constipation. *Acta Paediatr* 1998; **87**: 836-841
8 **Salminen S**, Salminen E. Lactulose, lactic acid bacteria, intestinal microecology and mucosal protection. *Scand J Gastroenterol Suppl* 1997; **222**: 45-48
9 **Picard C**, Fioramonti J, Francois A, Robinson T, Neant F, Matuchansky C. Review article: bifidobacteria as probiotic agents -- physiological effects and clinical benefits. *Aliment Pharmacol Ther* 2005; **22**: 495-512
10 **Agrawal A**, Houghton LA, Morris J, Reilly B, Guyonnet D, Goupil Feuillerat N, Schlumberger A, Jakob S, Whorwell PJ. Clinical trial: the effects of a fermented milk product containing Bifidobacterium lactis DN-173-010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2008; Epub ahead of print
11 **Higgins JPT**, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. In: The Cochrane Library, Issue 4. Chichester, UK: John Wiley & Sons, Ltd., 2006
12 **Koebnick C**, Wagner I, Leitzmann P, Stern U, Zunft HJ. Probiotic beverage containing Lactobacillus casei Shirota improves gastrointestinal symptoms in patients with chronic constipation. *Can J Gastroenterol* 2003; **17**: 655-659
13 **Möllenbrink M**, Bruckschen E. [Treatment of chronic constipation with physiologic Escherichia coli bacteria. Results of a clinical study of the effectiveness and tolerance of microbiological therapy with the E. coli Nissle 1917 strain (Mutaflor)] *Med Klin* (Munich) 1994; **89**: 587-593
14 **Yang YX**, He M, Hu G, Wei J, Pages P, Yang XH, Bourdu-Naturel S. Effect of a fermented milk containing Bifidobacterium lactis DN-173010 on Chinese constipated women. *World J Gastroenterol* 2008; **14**: 6237-6243
15 **Tabbers MM**, Chmielewska A, Roseboom MG, Boudet C, Perrin C, Szajewska H, Benninga MA. Effect of the consumption of a fermented dairy product containing Bifidobacterium lactis DN-173 010 on constipation in childhood: a multicentre randomised controlled trial (NTRTC: 1571). *BMC Pediatr* 2009; **9**: 22
16 **Bu LN**, Chang MH, Ni YH, Chen HL, Cheng CC. Lactobacillus casei rhamnosus Lcr35 in children with chronic constipation. *Pediatr Int* 2007; **49**: 485-490
17 **Banaszkiewicz A**, Szajewska H. Ineffectiveness of Lactobacillus GG as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. *J Pediatr* 2005; **146**: 364-369
18 **Banaszkiewicz A**, Szajewska H. Probiotics in the treatment of constipation: A systematic review of randomized controlled trials. *Pediatria Współczesna* 2005; **7**: 9-14
19 **Bekkali NL**, Bongers ME, Van den Berg MM, Liem O, Benninga MA. The role of a probiotics mixture in the treatment of childhood constipation: a pilot study. *Nutr J* 2007; **6**: 17
20 **Ouwehand AC**, Lagström H, Suomalainen T, Salminen S. Effect of probiotics on constipation, fecal azoreductase activity and fecal mucin content in the elderly. *Ann Nutr Metab* 2002; **46**: 159-162
21 **Bouvier M**, Meance S, Bouley C, Berta JL, Grimaud JC. Effects of consumption of a milk fermented by the probiotic Bifidobacterium animalis DN 173 010 on colonic transit time in healthy humans. *Biosci Microflora* 2001; **20**: 43-48
22 **Marteau P**, Cuillerier E, Meance S, Gerhardt MF, Myara A, Bouvier M, Bouley C, Tondu F, Bommelaer G, Grimaud JC. Bifidobacterium animalis strain DN-173 010 shortens the colonic transit time in healthy women: a double-blind, randomized, controlled study. *Aliment Pharmacol Ther* 2002; **16**: 587-593
23 **Meance S**, Cayuela C, Raimondi A, Turchet P, Lucas C, Antoine JM. Recent Advances in the Use of Functional Foods: Effects of the commercial fermented milk with bifidobacterium animalis strain dn-173 010 and yoghurt strains on gut transit time in the elderly. *Microb Ecol Health Dis* 2003; **15**: 15-22
24 Meance S, Cayuela C, Turchet P, Raimondi A, Lucas C, Antoine JM. A fermented milk with a bifidobacterium probiotic strain dn-173 010 shortened oro-fecal gut transit time in elderly. *Microb Ecol Health Dis* 2001; **13**: 217-222
25 **Alderson P**, Roberts I. Should journals publish systematic reviews that find no evidence to guide practice? Examples from injury research. *BMJ* 2000; **320**: 376-377

S- Editor Tian L **L- Editor** Stewart GJ **E- Editor** Ma WH