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ORIGINAL ARTICLE

Lactobacillus Species and Strains Effective on Symptoms of Irritable Bowel Syndrome

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ABSTRACT

IBS is one of the most prevalent gastrointestinal disorders (12-20% worldwide) with mostly unknown pathophysiology. There is question regarding role of intestinal flora and change in intestinal permeability in its pathogenesis. Numerous studies have been performed to show efficacy of probiotics in treatment of IBS. In this review study, it was attempted to accumulate information from best performed studies regarding use of lactobacillus for the treatment of IBS. This was a review study of RCT studies performed on the efficacy of Lactobacillus species in the treatment of IBS patients. All studies in the English language performed up to September of 2014 were searched in Pubmed, Google scholar, Wiley and Embase and Cochrane Database. In total 16 studies on efficacy of Lactobacillus probiotic or symbiotics were found for this review study with sample sizes of 24-214 participants. All studies were in favor of treatment groups except for one study on Lactobacillus plantarum MF 1298. Improvement in global symptoms was reported in seven studies and treatment success was reported in two studies. Six studies showed improvement in abdominal pain which included treatment with the single probiotics Lactobacillus plantarum 299v (DSM 9843) and Lactobacillus rhamnosus GG in two studies. Bloating was decreased in five studies in the treatment group including single probiotic Lactobacillus plantarum 299v (DSM 9843), and flatulence was decreased in one study which was mixed species treatment. Overall, studies agree with probiotic Lactobacillus and mixed species containing Lactobacillus improve symptoms in IBS patients. Studies have been limited in addressing degree of effectiveness of individual probiotics. Most trials are still small and effectiveness in various subtypes of IBS has not been evaluated. The same tools of measurement have not been used in most studies and quality of life has not been assessed in many studies which is important considering that IBS is a chronic disease and treatment is symptomatic and for improvement of functional status.

Keywords: *Lactobacillus, Probiotics, Irritable Bowel Syndrome, Symptoms, Randomized Controlled Study*

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INTRODUCTION

IBS is one of the most prevalent gastrointestinal disorders (12-20% worldwide). Various kinds of IBS by Rome III criteria are: diarrhea predominant, constipation predominant, alternating or mixed and undefined IBS (1). The features of irritable bowel syndrome are abdominal pain or discomfort relieved by defecation or gas release, alteration in bowel habits for at least 3 months. Its etiology appears to be multifactorial and its pathophysiology is mostly unknown. Genetic factors may have minor influence. Twenty to thirty five percent of all cases are post infectious which has lead to questioning the role of intestinal flora and change in intestinal permeability in its pathophysiology. It has been associated with female gender, stress and anxiety and has a wide range of differential diagnoses. Treatment has been directed at symptom control with lifestyle changes and variety of medications with efficacy of 35-45% (2). Three common IBS symptoms are abdominal pain, bloating or flatulence (3). In a study by Lembo et al, 60% of 443 IBS patients referred to a tertiary care center reported bloating as the symptom that bothered most and 29% considered abdominal pain as the most severe problem and flatulence was reported as one of the symptoms in 66% of patients (4, 5).

The concept of probiotics goes back to 1907 in publications of Metchinkoff who has proposed that lactobacilli suppress putrefying intestinal bacteria and subsequently, probiotics were defined in 1998 by Guarner et al. Probiotics are living organisms that ingesting them in certain numbers leads to health benefits beyond nutritional value. Later, it was introduced that these microorganisms modulate the immune system. Probiotics are usually certain types of Streptococcus, Lactobacilli, Bifidobacteria and E. Coli-Nisle 1917 and yeasts such as Saccharomyces boulardii, etc. Therapeutic advantages of one strain of probiotic cannot be extended to other strains and their efficacy needs to be studied (1). Lactobacilli and

Bifidobacteria and other commensal organisms are considered to be safe in general although concerns regarding use of massive doses in immunodepressed patients or those with intestinal resection exists (6). Additionally, 80 cases of bacteremia have been reported in Finland in individuals with severe prior comorbidity (7).

Mechanism of action of probiotics include: binding epithelium and producing substances that have antibiotic activity, competing for attachment and reducing invasion by other pathogens, affecting luminal immunity by changing cytokine and cellular profile from pro-inflammatory to anti-inflammatory, and converting carbohydrates to short chain fatty acids which provides nutrients to intestinal flora and affects motility (8, 9, 10).

Lactobacilli are members of the lactic acid producing bacteria and belong to the phylum Firmicutes. They are gram positive nonsporulating anaerobic bacteria. Lactobacilli require rich growth media and have key role in food fermentation. They are found in the human and animal GI tract and considered minor fecal microflora (0.01-0.6% of total bacterial counts). They also exist in the female urogenital tract. Best evidence exists regarding treatment and prevention of enteric infections and post antibiotic syndromes (11). Lactobacilli reside in the small intestine and stabilize gut microbiota in man and animals (12). L. rhamnosus GG is the most widely studied probiotic in children and adults. Orally at doses above 10^9 CFU/day, it at least temporarily colonizes the intestine and reduces diarrhea. Yet, in infants it has not decreased load of pathogens and it is of concern, it may have antagonistic activity (13).

Studies show variability in fecal composition among different IBS subtypes and healthy individuals; although consistent results have not been supported and also change with age and diet occurs (14). Probiotics are a diverse group of microorganisms that may help with balance of intestinal microflora. Numerous studies have been performed to show efficacy of these bioactive substances, yet there is lack of repeat studies and clarity of the most effective organisms in IBS patients. Lactobacilli are found in the human and animal GI tract, and it seems reasonable to select them as a probiotic for treatment of IBS patients. Therefore, in this review study it was attempted to accumulate information from best performed studies regarding use of lactobacillus for the treatment of IBS. It will be attempted to review repeat studies on some of the probiotic studies, gain insight to strains that are effective and review side effect profiles with use of certain Lactobacilli.

MATERIALS AND METHODS

This was a review study of RCT studies performed on the efficacy of Lactobacillus species in the treatment of IBS patients. All studies in the English language performed up to September of 2014 were searched in Pubmed, Google scholar, Wiley and Embase and Cochrane Database. Available studies on Lactobacillus preparations used for treatment of IBS were included. Search was performed on topics including microbiology and intestines and probiotics, bioactive microorganisms, probiotics and irritable bowel syndrome and RCTs, microorganisms and microbiota, gut microflora.

Inclusion criteria: RCT study with placebo comparison, Rome I, II, III criteria for diagnosis of IBD, adult and children studies, English language studies.

Exclusion criteria: Studies on probiotics other than Lactobacillus.

RESULTS

In total 16 studies were found, 14 for adults and 2 for children. All studies were RCTs that compared treatment with placebo. Studies were performed in various countries with sample sizes of 24-214. There were 6 studies on a single probiotic and 10 studies on symbiotics. Six of ten studies did not mention strain of microorganisms used. Statistical analysis was by intention to treat in 9 studies, not mentioned in 4 and per protocol in 3. Compliance with medication was mentioned and good in 4 studies. Follow up was reported only in one study at one month. Table 1 summarizes the results of the studies.

Table 1. Summary of Findings of RCT Studies on Lactobacillus Efficacy on IBS Symptoms

Study	Number of Patients	Probiotic	Results
Capello[15] et al 2013 (Italy)	n=64	Probinul: 5 gm twice a dayx 4weeks Lyophilized Each 5gm 5x 10^9 Lactobacillus plantarum 2x109 Lactobacillus casei spp rhamnosus	Inclusion in statistical analysis : not mentioned. Flatulance was reduced in symbiotic group compared to placebo ($P<0.05$). After treatment, longer rectosigmoid transit time and significant improvement in SF-36 scores were found in symbiotic group compared to placebo. The symptoms of bloating, pain and urgency was the same for treatment and placebo groups. Quality of life based on

		2x10⁹ Lactobacillus gasseri *1x10⁹ Bifidobacterium infantis* *1x 10⁹ Bifidobacterium longum* *1x10⁹ Lactobacillus acidophilus* *1x10⁹ Lactobacillus salivarus* *1x10⁹ Lactobacillus sporogenes* *5x10⁹ Steptococcus termophilus* (inulin)	short form-36 was significantly improved from pre to post treatment with symbiotic, but also in the placebo group in the domains of role-physical, bodily pain and mental health. Compliance >95% by diary. Side Effects: none reported.
Cui & Hu[16] 2012 (China)	n=60	Bifid triple viable capsules: 2 three times a dayx 4weeks Bifidobacterium longum Lactobacillus acidophilus	Inclusion in statistical analysis: not mentioned During intervention, the treatment group showed significantly more improvement in symptom severity score compared to placebo. Significant difference was not found between the two groups (probiotic and placebo) regarding dissatisfaction with defecation. After treatment, significant difference was found between the treatment and placebo groups on time and frequency of pain, discomfort, abdominal distention and dissatisfaction with bowel habits. Patients with diarrhea predominant IBS had low amounts of Bifidobacterium spp and Lactobacillus spp in stool samples compared to healthy individuals. Other IBS patients only had low amounts of Bifidobacterium spp. Side Effects and compliance not available.
Dapoigny[17] et al 2012 (France)	n=50	3 capsules (each 250mg) a dayx4 weeks Each capsule $2x10^8$ CFU per day Lactobacillus casei rhamnosus LCR35	Inclusion in statistical analysis: full analysis scale. In the total population, improvement in IBS severity score was not statistically different between LCR35 and placebo groups. Clinical response favoring LCR35 was found in patients with diarrhea-predominant IBS (not statistically significant). Eighty five percent of patients treated with LCR35 had Lactobacillus in their stools. Compliance not available. Side Effects: reported as none.
Ducrotte[18] et al 2012 (France)	n=214	One capsule a dayx4 weeks $10x10^9$ *Lactobacillus plantarum* 299v(DSM 9843)	Inclusion in statistical analysis: full analysis scale. Pain severity and daily frequency at the end of 4 weeks were lower in the treatment group compared to placebo ($P<0.05$). Bloating also showed similar results. Overall 78.1% of patients scored the probiotic effective on their symptoms as excellent or good compared to 8.1% for placebo ($P<0.01$). Decrease in abdominal pain frequency was significantly higher in probiotic group compared to placebo (51.9% versus 13.6%) as well as stool frequency, bloating and feeling of incomplete emptying. Mean severity of abdominal pain, bloating and feeling of incomplete emptying significantly decreased in treatment group more than the placebo group. Compliance not available. Side Effects: no significant side effects reported: One patient in probiotic group had vertigo.
Francavilla[19]	n=141 children	Lactobacillus rhamnosus GG	Inclusion in statistical analysis: intention to treat.

et al 2010 (Italy)	with functional abdominal pain	(LGG) 3x10^9 CFU twice a dayx 8 weeks	LGG led to decreased frequency and severity of abdominal pain compared to baseline (P<0.01 for both) but not placebo. Significant difference persisted at 8 weeks. After 12 weeks from start of treatment, 48/71 children in the LGG group had treatment success compared to 37/70 in the placebo group (P<0.03). LGG but not placebo led to significant decrease in number of patients with abnormal intestinal permeability testing (P<0.03). Effects were seen mainly in children with IBS. Compliance was 89% with probiotic and 86% with placebo. Side effects profile was not available.
Gawronska [20]et al 2006 (Poland)	n=104 children with functional dyspepsia, IBS or functional abdominal pain	Lactobacillus GG 3x10^9 twice a day x4 weeks	Inclusion in statistical analysis: intention to treat. The LGG group showed more treatment success (lack of pain) than placebo (25% versus 9.6%) relative benefit 2.6, 95% CI 1.05-6.6, number needed to treat 7, 95% CI 4-123. For IBS patients (n=37), the LGG group had more successful treatment compared to placebo, reduced frequency of pain but not severity (P=0.10). For the functional dyspepsia and functional abdominal pain groups no differences were noted. Compliance was not reported. Side effects: reported as none.
Jafari [21]et al 2014 (Iran)	n=108	Combination probiotic twice a day x 4 weeks *Bifidobacterium animalis subsp lactis BB-12* *Lactobacillus acidophilus LA-5* *Lactobacillus delbreuckii subsp bulgarius LBY-27* *Streptococcus thermophilus STY-31* With minimum potency per dose of 4x10^9 CFU	Inclusion in statistical analysis: intention to treat Overall, 85% of the symbiotic group noted general symptomatic relief compared to 47% of the control group (P<0.01). Abdominal bloating and pain were relieved significantly more with symbiotic than placebo. This effect decreased but remained significant at one month follow up, but not for feeling of incomplete defecation. Compliance was not reported Side effects: nausea, heartburn, borborygami, abdominal pain and distension which was not different from control group statistically.
Kajander[22] et al 2008 (Finland)	n=86	*Lactobacillus rhamnos GC* *L. rhamnosus LC 705* *Propionibacterium freudenreichii ssp shermani JS* *Bifidobacterium animalis ssp lactis* Bb12 Each 1x10^7 CFU/ml (1.2dl qd) for 5 months	Inclusion in statistical analysis: intention to treat Total IBS symptom score after treatment decreased more significantly in symbiotic compared to control (37% versus 9%, P=0.0083). Abdominal pain and distension were especially affected. Stool microbiota stability was higher in the probiotic compared to placebo group. Effect on CRP and cytokines was not observed. Compliance was not reported. Side effects: gastrointestinal or respiratory tract related, eye operation, atherosclerosis in carotid artery, inflamed mole, cystitis and tenosynovitis.
Kajander [23] et al 2005 (Finland)	n=103	Lactobacillus rhamnosus GG L. rhamnosus LC 705 Bifidobacterium breve Bb 99 Propionibacterium	Inclusion in statistical analysis: per protocol population who completed the study. At the end of treatment, there was 42% symptom reduction in symbiotic group compared to 6% in the

		freudenreickii ssp shermanii JS total amount of bacteria 8-9x10^9 CFU/day x 6 months	placebo. Borborygmi was milder in treatment group compared to placebo (p=0.008). Other symptoms did not show significant trend. Significant changes were seen in urgency and feeling of incomplete evacuation in symbiotic compared to placebo group. Health related quality of life score was decreased slightly in treatment group and increased in placebo. Compliance was 96% (by capsular return) Side effects profile was not available.
Kim et al 2003 (US)	n=25	Lyophilized bacteria: *Bifidobacterium (B. longum, B. infantis and B. breve)* *Lactobacillus (L. acidophilus, L. casei, L. bulgaricus and L. plantarum)* *Streptococcus (S. salivarius subspecies thermophilus)* 450x10^9 bacteria/day x 8 weeks	Inclusion in statistical analysis: intention to treat. Significant GI transit measurement, bowel function scores, or satisfactory global symptom relief was not found. Abdominal bloating was reduced (symbiotic -13.7 points, placebo -1.7 points, P=0.046). Symptoms were scored using visual analogue scale (100-mm). Compliance was not reported. Side effects: reported as none.
Lingaarden[24] et al 2010 (Norway)	n=16	*Lactobacillus plantarum* MF 1298 one capsule of 10^{10} CFU per day x two three-week periods with a four-week washout in between.	Inclusion in statistical analysis: modified intention to treat. Total IBS score was 6.44 in the probiotic group compared to 5.35 in the placebo group (P=0.010) which disfavored probiotic treatment. Mean number of weeks with satisfactory symptom relief with probiotic was significantly less than placebo (0.5 versus 1.44, P=0.006). Compliance was 95%. Side effects: nature of three minor side effects was not reported.
Lyra et al 2010 (Finland)	n=42	Multi species probiotic *L. rhamnosus* GG (ATCC 53103) *L. rhamnosus* LC 705 (DSM 7061, LC 705) *P. freundenreckii spp shermanii JS* (DSM 7067, PJS) B. breve Bb 99 (DSM 13692, Bb99) Total daily bacterial dose of 8-9x10^9 CFU	Inclusion in statistical analysis: not mentioned. Eight bacteria with possible role in IBS were evaluated in stool sample by PCR. Ruminococcus torque (94% phylotype similarity) remained abundant in the placebo group but decreased in the probiotic group. Also Clostridium thermosuccinogenes 85% remained elevated during intervention. Compliance was not reported. Side effects profile was not available.
Michael [25] & Kenche H. 2011 (US)	n=24 IBS patients with diarrhea predominance	VSL#3 900x10^9 bacteria per day for 8 weeks.	Inclusion in statistical analysis: not mentioned. Improvement in satiety was found in treatment group. Intestinal flora by 16sRNA detection did not show change. Compliance was not reported. Side effects profile was not available.
Murakami[26] et al 2012 (Japan)	n=35	Lactobacillus brevis KB 290 one capsule (≥10^{10} CFU/capsule) a day for 4 weeks, stopped for 4 weeks and administered oppositely for 4 weeks	Inclusion in statistical analysis: as per protocol. Significant difference in IBS symptoms was not found during various periods, but mean quality of life scores improved during test capsule consumption. Also frequency of watery and musky stools and abdominal

			pain were significantly lower during test capsule consumption. Stool samples analyzed by T-RFLP showed significantly higher Bifidobacterium and lower clostridium after test capsule use compared to placebo. Compliance was not reported. Side effects profile was not available.
Roberts[27] et al 2013 (England)	n=179 IBS patients with constipation element	Yogurt product containing *Bifidobacterium lactis* (I-2494) $1.25x10^{10}$ CFU *S. thermophilus* (French strain I-1630) and L. bulgaris (French strain I-1632, I-1519) $1.2x10^{9}$ CFU per cup two times a day for 12 weeks	Inclusion in statistical analysis: intention to treat. Significant difference between groups at 4 weeks was not observed in symptoms of IBS. By week 8, 46% of treatment group versus 68% of placebo reported sufficient relief (P=0.03) which persisted at 12 week. High dropout rate due to dislike of product taste and nausea was reported. Compliance was not reported.
Yoon[28] et al 2014 (Korea)	n=49	Multispecies probiotic *Bifidobacterium longum* *B. bifidum* *B. lactis* *Lactobacillus acidophilus* *L. rhamnosus* *Streptococcus thermophilus* Each capsule $5x10^{9}$ viable cells twice daily x 4 weeks	Inclusion in statistical analysis: intention to treat. Proportion of patients with improved IBS symptoms at 4 weeks was significantly higher in symbiotic compared to placebo (68.0% versus 37.5%, P<0.05). Only treatment and not placebo group showed improvement in abdominal pain/discomfort and bloating. Change in abdominal pain was not statistically significant. Fecal analysis by PCR showed that B. lactis, L. rhamnosus and S. thermophilus increased significantly in the treatment group and B. lactis increased in placebo group. Compliance was not reported. Side effect profile was not available.

DISCUSSION

In total 16 studies on efficacy of Lactobacillus probiotic or symbiotics were found for this review study with sample sizes of 24-214 participants. All studies were in favor of treatment groups except for one study on *Lactobacillus plantarum* MF 1298 [24]. Improvement in global symptoms was reported in 7 studies [16, 18, 21, 22, 23, 27, 28] and treatment success was reported in two studies [19, 20]. The above agrees with a meta-analytic study performed evaluating efficacy studies of probiotics in IBS. Twenty trials were included in the analysis from 1982-2007. Probiotic use improved global IBS symptoms compared to placebo (pooled relative risk 0.77, 95% CI 0.62-0.94). They were also associated with less abdominal pain in comparison with placebo (RR pooled=0.78, 0.69-0.88) [3]. In another meta-analysis of studies up to the year 2007, 14 RCT's were identified. Results showed a modest improvement in overall symptoms after treatment for several weeks. Seven trials with dichotomous data showed OR 1.6 (95% CI 1.2 to 2.2), for six trials with continuous data standardized mean difference was 0.23 (95% CI 0.07 to 0.38) [29].

Six studies showed improvement in abdominal pain which included treatment with the single probiotics *Lactobacillus plantarum* 299v (DSM 9843) [18] and *Lactobacillus rhamnosus* GG in two studies [19, 20]. Bloating was decreased in 5 studies in the treatment group including single probiotic *Lactobacillus plantarum* 299v (DSM 9843) (18), and flatulence was decreased in one study which was mixed species treatment. This agrees with a meta-analysis study by Ortiz-Lucas and colleagues where *L. plantarum* was noted for improving distension [30].

Psychological assessment with quality of life measures was performed in a few of the studies. Improvement was seen in 2 studies [15, 26] and worsening in one [23]. This assessment is important to be included in studies as IBS is a chronic disease and treatment is mainly symptomatic and functional.

Stool bacteria were evaluated in 4 studies. In one study with mixed species treatment, Stool microbiota stability was higher in the probiotic compared to placebo group [22]. In another study with mixed species treatment, *Ruminococcus* torque (94% phylotype similarity) remained abundant in the placebo group but

decreased in the probiotic group. Also *Clostridium thermosuccinogenes* 85% remained elevated during intervention [31]. In a study with single probiotic Lactobacillus brevis KB 290 treatment, Stool samples analyzed by T-RFLP showed significantly higher *Bifidobacterium* and lower clostridium after test capsule use compared to placebo [26]. In another study reviewed with mixed species treatment, fecal analysis by PCR showed that *B. lactis*, *L. rhamnosus* and S. *thermophilus* increased significantly in the treatment group and B. lactis increased in placebo group. The placebo effect was contributed to dietary intake [28]. The above agree with studies regarding variability in fecal composition among different IBS subtypes and healthy individuals; although consistent results have not been supported and also change with age and diet occurs [14]. C. *thermosuccinogenes* 85 has been shown to be associated with IBS-mixed patients and healthy controls compared to IBS-diarrhea predominant. The R. torques 94% phylotype has been associated with IBS-diarrhea predominant [32,31]. Previous studies show higher counts of anaerobic organisms such as clostridium in stool cultures of IBS patients compared to controls [3]. It has been shown that amount of R. torques was positively correlated with severity of IBS symptoms reported by patients [34].

Side effect profile showed none reported in 4 studies, present in 4 studies and not available in 8. Treatment duration in studies that reported side effects were 4 weeks, 4 weeks, 5 months, and total of 6 weeks (with in between wash out period) [18, 21, 22, 24]. Most side effects were reported in the 5 month treatment group where the duration of treatment can explain why side effects appeared even though lower dosages of probiota were used. Side effects were reported in both single and mixed species studies which included vertigo, GI symptoms, respiratory system symptoms, eye operation, coronary artery disease, inflammatory conditions and cystitis. The above agrees with adverse events reported in a meta-analysis study were dyspepsia, headache, nausea were reported and nature of events in some studies were not given. In another meta-analysis, adverse effects were reported as few and not serious and similar in treatment and control groups. Recommendations were considering variables such as predominance of GI symptoms, obtaining microbiological profile and psychological profile [30].

Limitations of this study were few studies were obtained where single probiotics were evaluated for efficacy and safety. Tools for comparison were not the same across the studies to be able to evaluate efficacy amounts.

Overall, studies agree with probiotic Lactobacillus and mixed species containing Lactobacillus improve symptoms in IBS patients. Studies have been limited in addressing effectiveness of individual probiotics. Most trials are still small and effectiveness in various subtypes of IBS have not been evaluated. The same tools of measurement have not been used in most studies and quality of life has not been assessed in many studies which is important considering that IBS is a chronic disease and treatment is symptomatic and for improvement of functional status. For future studies, consideration of the above and comparison with other medical treatments is suggested.

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