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Do Probiotics Provide Adequate Relief From Overall Symptoms, Including Abdominal Pain and Bloating, in Adults With Irritable Bowel Syndrome?

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not probiotics provide adequate relief from overall symptoms of irritable bowel syndrome including abdominal pain and bloating in adults with irritable bowel syndrome.

Study Design: Review of three published randomized, double blind, placebo controlled clinical trials were used for this review. The articles were found on PubMed and EBSCOhost web, and were selected based on outcomes measured and relevance to the objective.

Outcomes Measured: The outcomes were measured by a 10-point visual analog scale for each symptom, or daily dairy entries addressing overall symptom relief, and a questionnaire at the beginning and end of the trial for overall quality of life.

Results: The Ki Cha, et al. study proved a statistically significant improvement in the adequate relief of symptoms of IBS, including abdominal pain and bloating, however the Roberts, et al. and the Cappello, et al. studies did not show a statistically significant improvement of symptoms in the probiotic group as compared to the placebo group.

Conclusions: Based on the three randomized, double blind, placebo controlled clinical trials the efficacy of treating irritable bowel syndrome with probiotics is inconclusive. Future studies should focus on the efficacy of probiotics in a specific subtype of IBS, for example only focus on constipation predominate irritable bowel syndrome, to help determine if probiotics are a reasonable intervention for a specific subtype of irritable bowel syndrome.

Key Words: Irritable Bowel Syndrome, Probiotics

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic disorder of the gastrointestinal tract which causes changes in bowel habits or stool consistency leading to nonspecific symptoms including: abdominal pain, bloating, changes in bowel habits including diarrhea and/or constipation, dyspepsia, nausea, early satiety, urinary urgency, frequency, and chest pain; however, the mainstay of diagnosis is the ROME III criteria which states that IBS can be diagnosed if the patient suffers from recurrent, chronic abdominal pain for at least three days per month for at least three months associated with two of the following: improvement with defecation, onset associated with change in frequency of stools, and onset associated with change in appearance of stool. The condition is classified as either constipation predominate, diarrhea predominate, or mixed based off the bowel movements of the patient. The wide array of symptoms negatively impact the patients quality of life and is the second leading reason for absence from work after the common cold. The syndrome effects all ages and races, however women are more commonly affected than men.[1]

IBS is classified as a functional bowel disorder because the symptoms occur in the mid to lower gastrointestinal tract and cannot be attributed to any underlying structural or biochemical abnormalities.[2] Therefore the cause of irritable bowel syndrome is unknown, however the theories proposed about the etiology are as follows: gastrointestinal motility, visceral hypersensitivity, intestinal inflammation, alterations in fecal micro flora, bacterial overgrowth, and food sensitivity.[3]

Of the functional bowel disorders, IBS is the most common affecting 10-15% of the North American population. The estimated annual healthcare cost of IBS is $30 billion. The

exact number of healthcare visits each year due to irritable bowel syndrome is unknown, however the diagnosis accounts for 25-50% of gastrointestinal referrals.[1]

There is no gold standard treatment for IBS because no method for treatment has been proven to help all patients with the condition. The initial therapy for a patient with IBS is patient education, dietary modification, reducing intake of gas producing foods, and increase in physical activity.[1] The goal of the provider during the initial therapies is to build an alliance with the patient and help the patient understand IBS is a chronic condition.[4]

For moderate to severe symptoms adjunctive pharmacotherapies aimed at relieving specific symptoms may be helpful. For abdominal pain, providers may use antispasmodics such as dicyclomine and hyocyamine, tricyclic antidepressants (TCA) such as amitriptyline, nortriptyline, and imipramine, and antibiotics such as rifaximin. For constipation predominate IBS therapies include laxatives such as polyethylene glycol (PEG), lactulose, or milk of magnesium, chloride channel activators such as Lubiprostone, or guanylate cyclase agonists such as Linaclotide. For diarrhea predominate medical interventions include antidiarrheal agents such as loperamide, or bile acid sequestrantes such as cholestyramine, colestipol, and colesevelam.[4]

There is no cure for the IBS but the goal of treatment is to control the symptoms. The above therapies have shown improvement for some patients, but there is no standard of care. Probiotics have been reported to help some patients especially with controlling the bloating associated with IBS, however, there is no proven method for symptom control.[4]

OBJECTIVE

The objective of this selective systematic review is to determine whether or not probiotics provide adequate relief from overall symptoms of irritable bowel syndrome including abdominal pain and bloating in adults with irritable bowel syndrome.

METHODS

Criteria used for selection of articles for this systematic review was based on the population age, the intervention, and the outcomes measured. The populations of the research groups in all the articles were adults, both males and females, ages 18 to 65 years old, diagnosed with either constipation predominate or diarrhea predominate irritable bowel syndrome. All the studies compared the outcomes using an oral probiotic to a visually matched placebo. One of the articles used a yogurt-like product instead of a tablet or capsule for administration of the probiotic or placebo.[5] The articles addressed patient-oriented evidence that matters, which included the adequate relief of the symptoms of abdominal pain and bloating.

PubMed and EBSCOhost web were used to search for double-blind, randomized-controlled trials published in peer-reviewed journals in the last five years in the English language. The important key words used when searching for the articles were "irritable bowel syndrome" and "probiotics". The articles were selected based on their relevance to the objective of this systematic review, the participant groups of patients greater than 18 years old, whether or not they evaluated patient-oriented evidence that matters. The exclusion criteria for the articles included papers that included patients under the age of 18 years old, articles that were not randomized, double blind, placebo controlled clinical trials, and trials that addressed disease-oriented evidence. The statistics reported in the studies included p-values. The relative risk reduction (RRR), absolute risk reduction (ARR), and numbers needed to treat (NNT) were calculated for each article using dichotomous data in order to support the efficacy of use of probiotics for the relief of symptoms as compared to the placebo group.

OUTCOMES MEASURED

All of the articles addressed the outcome of symptom relief from abdominal pain and bloating as well as overall improvement in quality of life. Ki Cha, et al. measured adequate relief from IBS symptoms including abdominal pain, loose stool, urgency, mucus in stool, bloating, passage of gas; stool frequency and consistency; and quality of life including dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual function, and impact on relationships. Adequate relief from IBS symptoms were assessed by 10-point visual analog scale for each symptom daily, and quality of life was assessed at the beginning and end of the trial by a questionnaire. Stool frequency was measured by stools per day, and consistency was measured by the Bristol Stool Scale.[6]

Roberts, et al. measured overall symptom relief and specific symptom relief including bloating, abdominal pain and flatulence, stool consistency and frequency, and quality of life. The outcomes of overall symptom relief were measured by weekly diary entries which included ratings of overall symptom relief and specific symptom relief including bloating, abdominal pain and flatulence. Stool consistency and frequency was assessed using daily symptom diaries, returned at weeks 4, 8, 12, in which the entries included stool consistency and frequency, and bowel movement difficulty. To assess participants' quality of life the Birmingham IBS Symptom Score, IBS SSS, and IBS specific quality of life tool was used.[5]

Cappello, et al. (2013) measured IBS symptom relief including bloating, sensation of flatulence, pain and fecal urgency; colonic transit time, stool consistency and sensation of incomplete evacuation; and quality of life including physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional, and mental health. The IBS symptoms were assessed by a daily diary, stool consistency was evaluated on the Bristol stool scale,

sensation of incomplete evacuation was assessed on a binomial answer and bowel symptoms were assessed on 100-mm VAS, at the end of every week patients answered yes or no to whether they had relief from bloating, pain, sensation of flatulence, and fecal urgency. Colonic transit time was assessed via serial abdominal X-rays, and quality of life was assessed by the SF-36 questionnaire which was completed by participants at beginning and end of the trial.[7]

This systematic review focuses on the overall relief of the symptoms of abdominal pain and bloating in adults diagnosed with irritable bowel syndrome.

Table 1 – Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/d	Interventions
Ki Cha[1] (2012)	RCT	50	18-65	Men and women between ages 18 and 65 years old with diarrhea dominant IBS	Constipation-or mixed-type IBS; Lactose intolerance; Pregnancy; Severe illness; Psychiatric disorder; Abdominal surgery; Participation in clinical trial within 3 months	3	Duolac7 (*L. acidophilus, L. plantarum, L. rhamnosus, B. breve, B. longum, S. thermophiles*)
Roberts[2] (2013)	RCT	179	18-65	IBS dx > 6 months; Meet ROME III criteria; with a constipation element IBS	Terminal stage of illness; Mental illness; Passing 3 or more soft stools per day; pregnant, breast-feeding, lactose intolerant	76	Product containing *B. lactis, S. thermophilus, L. bulgaricus*
Cappello[3] (2013)	RCT	68	18-75	Patients with average daily abdominal bloating score of $\geq$ to 24 on a 100mm VAS during 2-week run-in period	Pregnancy; Unstable medical condition; IDDM; psychiatric diagnosis; history of substance abuse; abdominal surgery; use of medications altering GI motility	4	Mixture containing *L. plantarum, L. casei rhamnosus, L. gasseri, B. infantis, B. longum, L. acidophilus, L. salivarus, L. sporogenes, S. termophilus*

RESULTS

Three randomized, double blind, placebo controlled clinical trials were used in this systematic review to determine the efficacy of probiotics for the treatment of IBS symptoms in adults. The data presented in the articles was dichotomous, and the trials were conducted based on intention-to-treat analysis of the data. The following information will only take into account the data from each article on adequate relief from abdominal pain and bloating.

In the Ki Cha, et al. study 60 patients met the inclusion criteria for the study. Of the 60 participants, nine withdrew from the study and one person was excluded due to a positive pregnancy test. Therefore 50 participants were randomized into the experimental and control groups and received daily oral treatment in the form of a capsule for eight weeks. During the study one participant dropped out of the probiotic group and two participants dropped out of the placebo group, therefore 47 people completed the study: 24 patients in probiotics group and 23 patients in the placebo group. The outcomes of symptom relief were evaluated weekly for ten weeks, and the compliance rate for the study was reported at greater than 80%. The weekly diary entries of symptom relief showed a significant difference in adequate relief between the placebo group and the probiotic group. The proportion of participants in the probiotic group that had adequate symptom relief was 48% whereas 12% of the placebo group had adequate relief (Table 2). Therefore there was a statistically significant decrease in IBS symptoms including abdominal pain and bloating achieved using a probiotic versus a placebo ($p=0.01$).[6]

Table 2: Percent of Participants with Adequate Relief of Symptoms after 8 Weeks of Treatment[6]

	# of participants in group	# of participants with adequate relief	% of participants with adequate relief of symptoms
Probiotic	25	12	48%
Placebo	25	3	12%

This data shows that the control event rate (CER), which included the placebo group is 12%, whereas the experimental event rate (EER), which included the probiotic group is 48%. The relative risk reduction (RRR) was calculated to be 3%, and the absolute risk reduction (ARR) was calculated to be 36%. From this data the numbers needed to treat was determined to be 3, therefore for every 3 people with IBS who are treated with a probiotic 1 more patient will have relief from their symptoms than the placebo at 8 weeks.

In the Roberts, et al. study 179 participants were randomized into the experimental and control groups and received daily oral treatment in the form of a yogurt product for twelve weeks. A large dropout rate occurred during the study due to various issues with the participants including distaste for the product and personal factors. Only 81 people completed the study: 48 patients in probiotics group and 33 patients in the placebo group. The outcomes of symptom relief were evaluated weekly for twelve weeks via weekly dairy entries of symptom relief. The diary entries were evaluated at weeks 4, 8, and 12. The data showed a significant difference in adequate relief between the placebo group and the probiotic group. The proportion of participants in the experimental group that had adequate symptom relief was 45.8% whereas the proportion of the placebo group experiencing adequate relief was 75.8% (Table 3). Therefore there was a statistically significant decrease in IBS symptoms including abdominal pain and bloating achieved in the placebo group verses the probiotic group ($p=0.004$).[5]

Table 3: Percent of Participants with Adequate Relief of Symptoms after 12 Weeks of Treatment[5]

	# of participants with adequate relief	% of participants with adequate relief of symptoms
Probiotic	48	45.8%
Placebo	33	75.8%

This data shows that the control event rate (CER), which included the placebo group is 75.8%, whereas the experimental event rate (EER), which included the probiotic group is 45.8%. The relative risk reduction (RRR) was calculated to be -40%, and the absolute risk reduction (ARR) was calculated to be -30%. From this data the numbers needed to treat was determined to be -3, therefore for every 3 people with IBS who are treated with a probiotic, 1 fewer patient will have relief from their symptoms when compared to the placebo. There was a statistically significant decrease in IBS symptoms including abdominal pain and bloating, however the improvement of symptoms was reported to be higher in the placebo group versus the probiotic group. This proves a probiotic does not reduce an IBS patient's overall symptoms.

In the Cappello, et al. study 68 participants were randomized into the experimental and control groups and received daily oral treatment in the form of a powder dissolved in water and taken twice a day for twelve weeks. During the study there were 4 dropouts in the probiotic group and 4 drops outs in the placebo group, therefore 64 people completed the study: 32 patients in probiotics group and 32 patients in the placebo group. The outcomes of symptom relief were evaluated via a daily symptom diary for four weeks, and the compliance rate was greater than 80% in the study. The proportion of participants in the experimental group that had adequate symptom relief was 46.9% whereas the proportion of the placebo group experiencing adequate relief was 65.6% (Table 4). Therefore the data did not show a significant difference in adequate relief between the placebo group and the probiotic group ($p=0.21$).[7]

Table 4: Percent of Participants with Adequate Relief of Symptoms after 4 Weeks of Treatment[7]

	# of participants in group	# of participants with adequate relief	% of participants with adequate relief of symptoms
Probiotic	32	15	46.9%
Placebo	32	21	65.6%

This data shows that the control event rate (CER), which included the placebo group is 65.6%, whereas the experimental event rate (EER), which included the probiotic group is 46.9%. The relative risk reduction (RRR) was calculated to be -28.5%, and the absolute risk reduction (ARR) was calculated to be -18.7%. From this data the numbers needed to treat was determined to be -5, therefore for every 5 people with IBS who are treated with a probiotic, 1 fewer patient will have relief from their symptoms when compared to the placebo. There was not a statistically significant decrease in IBS symptoms including abdominal bloating using a probiotic versus a placebo. This proves that a probiotic does not reduce an IBS patient's symptoms of abdominal bloating.

In all three studies patients suffered minimal adverse effects. In the Roberts, et al. study some participants reported nausea due to the intervention which led to them dropping out of the study.[5] In the Ki Cha, et al. study there were two participants who reported worsening abdominal pain and bloating in the placebo group, but no adverse events reported in the probiotic group.[6] In the Cappello, et al. study there was no adverse events reported.[7]

DISCUSSION

This systematic review compares three randomized, double blind, placebo controlled clinical trials in which the Ki Cha, et al. trial proved that probiotics can be helpful in treating the symptoms of IBS, however the other two trials showed there was no clinically significant difference in relief of symptoms between the probiotic and placebo groups.[5,6,7] In the Ki Cha, et al. article only patients with diarrhea predominate IBS were included in the trial, therefore it is possible probiotics are more helpful in treating the symptoms of diarrhea predominate IBS and less helpful in the treatment of constipation predominate or mixed IBS.[6]

Probiotics are currently used to treat certain allergies, such as eczema, and infections especially infections of the vagina such as yeast infections. A problem with the use of probiotics is that probiotics are not FDA regulated therefore the consumer may purchase different strain of the bacteria than they had anticipated. Also the dose of the probiotic may be higher or lower than the patient expected.[8]

One of the limitations of the Roberts, et al. study was a high dropout rate. In this trial there was a dropout rate of approximately 55%.[5] Additionally all three of the trials only used one dose of the probiotic for all participants, while other patients may have needed higher doses in order for there to be improvement of their symptoms. Another limitation for all three studies was small sample sizes.[5,6,7] A limitation of the Cappello, et al. trial was a short follow up time period. This study only followed patient for four weeks, however if the participants were followed longer the trial may have shown more improvement of symptoms in the probiotic group.[7]

CONCULSION

In conclusion, the three randomized, double blind, placebo controlled clinical trials in this systematic review demonstrated that the data pertaining to the efficacy of treating irritable bowel syndrome with probiotics is inconclusive. The Ki Cha, et al. study proved a statistically significant improvement in the adequate relief of symptoms of IBS, including abdominal pain and bloating, however the Roberts, et al. and the Cappello, et al. studies did not show a statistically significant improvement of symptoms in the probiotic group as compared to the placebo group.[5,6,7]

In future studies it would be useful if the study only looked at one subtype of IBS instead of including all subtypes, diarrhea predominate, constipation predominate, and mixed. This

would be helpful in determining whether probiotics would be helpful in the treatment of all three subtypes or only a viable treatment for one of the subtypes. Furthermore, there still needs to be more research into the efficacy of probiotics in the treatment of other conditions including irritable bowel syndrome.

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