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**Does The Use Of Probiotics Treat Abdominal Pain In Children
Between The Ages Of 4 And 18 With Irritable Bowel
Syndrome?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

OBJECTIVE: The objective of this selective EBM review is to determine whether or not the use of probiotics treat abdominal pain in children between the ages of 4 and 18 with irritable bowel syndrome.

STUDY DESIGN: Systemic review of three randomized controlled trials (RCTs) published after 2007, all English language.

DATA SOURCES: All three randomized controlled trials were found on PubMed and were selected based on relevance to the proposed clinical question.

OUTCOMES MEASURED: Main outcomes measured were duration with and without abdominal pain, severity of pain, postprandial swelling, belching-abdominal distention, difficulty in defecation, urgent defecation, and feeling of incomplete defecation. Outcomes were measured by using Wonger-Baker FACES pain rating scale, five-point likert scale, and a self-reported questionnaire.

RESULTS: Two studies found no significant improvement in abdominal pain or discomfort when comparing probiotics to placebo when treating irritable bowel syndrome. One study found a significant improvement in abdominal pain when comparing probiotics to placebo. When looking at efficacy of probiotics, two studies had a relatively low number needed to treat.

CONCLUSION: From the three randomized controlled trials, it can be concluded that treating children with irritable bowel syndrome between the age of 4 and 16 with probiotics is inconclusive. Further research is warranted.

KEY WORDS: Irritable bowel syndrome and probiotics

INTRODUCTION:

Irritable bowel syndrome, according to Rome III criteria, is defined as abdominal pain or discomfort associated with relief after defecation, change in stool frequency and/or a change in stool consistence.¹ According to the National Institute of Diabetes and Digestive and Kidney Disease, IBS is diagnosed when a child, who is growing as expected, has abdominal pain or discomfort once per week for at least 2 months without other disease or injury that could explain the pain.² IBS has varying symptoms including cramping, bloating, diarrhea, constipation, or alternating diarrhea and constipation. IBS is not life-threatening but can impact daily activities and quality of life.³

Irritable bowel syndrome is the most common gastrointestinal diagnosis among gastroenterology practices in the United States.² It is also one of the top 10 reasons patients visit their primary care physician.² According to reported studies, the disease prevalence is lower in the Hispanic, Asian and black population.³ In a pediatric population, males and females are equally affected.³ IBS symptoms are reported in 14% of high-school students and 6% of middle-school students.³ Irritable bowel syndrome is not described in preschool-aged or in younger children because the diagnosis depends on the child's ability to report detailed symptoms.³ Children who have a history of recurrent abdominal pain are at increased risk of developing IBS in the future.²

Due to high prevalence of this condition, there is a definite economic burden in the United States. The exact number of pediatric visits per year is unknown but in the general population there are between 2.4 and 3.5 million annual visits.^{3,4} Not all individuals with IBS symptoms obtain medical care.⁴ Most physicians diagnose IBS using diagnosis of exclusion because there are no diagnostic studies available. Using this method to diagnose IBS leads to

extensive and unnecessary testing.⁵ The direct cost for the general population has been estimated to range from \$1.5 to \$10 billion per year.⁵ These figures do not take into account prescriptions and over-the-counter medications which can further increase the expenditure. The indirect cost of IBS has been estimated to be much greater, approaching \$20 billion per year.⁵

The cause of IBS is unknown. Researchers believe a combination of physical and abnormal psychotic disorders can lead to irritable bowel syndrome.² Possible causes of IBS in children include signal disruption between the brain and GI tract, abnormal GI motility, hypersensitivity to abdominal pain, anxiety, depression, bacterial gastroenteritis, small intestinal bacterial overgrowth, and genetics.²

Irritable bowel syndrome is not a disease; it is a group of symptoms that occur together.² Unfortunately there is no cure for IBS. Treatment is based on symptoms patients are experiencing. Symptoms can be treated with dietary changes, medication, probiotics, and therapy.² Medications commonly used include fiber supplements, laxatives, antidiarrheals, antispasmodics, and antidepressants. Cognitive behavioral therapy, psychodynamic/interpersonal therapy, and hypnotherapy can help reduce stress and improve IBS symptoms.²

Probiotics have multiple beneficial effects in the gastrointestinal tract, such as increasing the mass of bacterial microflora, decreasing bacterial overgrowth, inducing the intestinal mucosal barrier, and normalizing the motility of the digestive tract.⁶ Also, they can regulate the balance between the pro- and anti-inflammatory cytokines.⁶ Due to these beneficial effects, probiotics have been suggested as a therapeutic option for IBS.⁶ Studies have found that probiotics, specifically Bifidobacteria and certain probiotic combinations, improve symptoms of IBS when taken in large amounts.²

OBJECTIVE:

The objective of this selective EBM review is to determine whether or not the use of probiotics treat abdominal pain in children between the ages of 4 and 18 with irritable bowel syndrome.

METHODS

Three double-blind randomized controlled trials (RCTs) were used in this review. The population studied included patients between the ages of 4 and 18 with irritable bowel syndrome. The intervention used in all three RCTs was probiotics. The populations were compared to a control group who were given a placebo. Outcomes measured in the study included abdominal pain and abdominal discomfort.

“Irritable bowel syndrome” and “probiotics” were keywords used to narrow the search on PubMed. All articles were published in English and in peer-reviewed journals. Articles were selected by relevance to the clinical question and had patient oriented results (POEM). Studies that were POEM’s, randomized controlled trials, and published after 2007 were included. Cochrane systemic reviews, meta-analysis’s, and patients over the age of 18 were excluded. Statistics used were relative risk reduction (RRR), absolute risk reduction (ARR), numbers needed to treat (NNT), p-value, and mean change from baseline. Table 1 demonstrates the demographics and characteristics of the reviewed studies.

Table 1: Demographics and characteristics of included studies

Study	Type	#pts	Age (yrs.)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Basturk ⁷ (2016)	RCT	71	4-16	Patients who were diagnosed with IBS according to the Rome III criteria in the Akdeniz University Pediatric Gastroenterology outpatient clinic between September 2014-May 2015.	Patients who are not diagnosed with IBS.	5	Probiotic treatment (5 x 10 ⁹ CFU B. Lactis) BID PO x 4 weeks.
Jadresin ¹ (2016)	RCT	55	4-18	Patients who were diagnosed with functional abdominal pain and IBS at the children's hospital Zagreg from May 2012-December 2014	Patients with underlying diseases or has been treated with an antibiotic/probiotic 7 days prior to enrollment.	9	Probiotic: citrus flavored 450mg chewable tablet qd x 12 weeks. The total value count of L. reuteri was 1 x 10 ⁸ live bacteria (CFU)/tablet
Kianifar ⁶ (2015)	RCT	60	4-18	Patients who were diagnosed with IBS by a pediatric gastroenterologist and have had active symptoms of abdominal pain for at least 2 weeks prior to the start of the study.	Patients with underlying diseases or taking any medications	8	Probiotic capsule that contained LGG at a concentration of 1x 10 ¹⁰ cfu/ml bacteria and inulin. BID x 4 weeks.

OUTCOMES MEASURED

The Basturk et al study, evaluated outcomes such as postprandial swelling, belching-abdominal distention, difficulty in defecation, urgent defecation, and feeling of incomplete defecation. A self-reported questionnaire was used prior to treatment and post treatment. Patients with improvement in all presenting symptoms were accepted as ‘fully benefited’ and those who had resolution in one or several symptoms were accepted as ‘partially benefited’.¹

The outcome from Kianifar et al, study evaluated severity of pain. A five-Likert scale was used to specify the severity of the pain (0=very mild, 1= mild, 2= moderate, 3= severe, 4= very severe).⁶ From both groups, outcomes were measured (placebo and probiotic) prior to treatment and weekly for four weeks. Intervention lasted for four weeks.

Patients in the Jadresein et al study were given a diary to rate severity of pain on a daily basis. The probiotic and placebo were discontinued after twelve weeks but rating severity of pain daily continued for another four weeks. Even though patients were asked to record daily, they were required to visit a certain hospital for evaluation on month one, three, and four. Symptoms were evaluated using a faces scale (Wong-Baker FACES Pain Rating Scale; 0-no hurt-10 hurts worst) for pain.¹

RESULTS

Basturk et al study, included children between the ages of 4 and 16 years who were diagnosed with IBS according to the Rome III criteria in the Akdeniz University Pediatric Gastroenterology outpatient clinic between September 2014 and May 2015.⁷ The study did not report an exclusion criteria for selecting patients. Family members of each patient disclosed a written informed consent. Trial was double-blinded; forty-eight patients were randomized into an experimental and control group. The experimental group which consisted of twenty-four patients

received a probiotic (5×10^9 CFU *B. lactis*) twice a day for four weeks. The control group which had twenty-four patients were given a placebo (900mg of inulin) twice a day for four weeks. Self-reported questionnaires were used to evaluate the efficacy of probiotics in treating IBS. Initially, there was no significant difference in symptoms between both groups.⁷ Chi-square test was used to analyze the collected data from the self-reported questionnaire. In the probiotic group, the most significant improvement observed was belching-abdominal fullness ($p < 0.001$), while there were also significant improvements in bloating after meals ($p = 0.016$), and difficulty with defecation ($p = 0.031$).⁷ Full recovery was observed in seven patients (29.2%) in the probiotic group and three patients in the placebo group (12.5%).⁷ When the groups were compared with each other with regards to full recovery, there were no significant difference between the prebiotics and probiotics, $p = 0.155$.⁷ Table 2 demonstrates the statistical significance between both groups. Data demonstrated relative risk reduction of 45% and absolute risk reduction of 21%. NNT is -4. NNT, numbers needed to treat, means for every 4 children treated with probiotics it would prevent one fewer child from experiencing excruciating abdominal pain, compared to the control group.

Table 2: Statistical significance at baseline and 4 weeks, belching-abdominal fullness

	Before	After	p-value
Probiotics (n=24)	75%	25%	<0.001*
Placebo (n=24)	54.2%	45.8%	0.250

Chi-square test was used.

*p-value ≤ 0.05 is significant

Table 3: Efficacy of Basturk et al⁷ study.

% of participants, within the comparison group, who experienced belching-abdominal full after 4 weeks (CER)	% of participants, within interventional group, who experienced belching-abdominal full after 4 weeks (EER)	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	Numbers needed to harm (NNT)
45.8%	25%	45%	21%	-4 patients

In the Kianifar et al study, the inclusion criteria were patients age 4 to 18 years old who had active symptoms of abdominal pain for at least two weeks before the beginning of the study and had been diagnosed with IBS by a pediatric gastroenterologist.⁶ The diagnosis must have been made on the basis of Rome III criteria and other differential diagnosis must have been excluded by laboratory evaluation, abdominal ultrasound, radiographic imaging, endoscopy, and breath hydrogen testing.⁶ Patients who are currently taking drugs or had an underlying disease such as cardiac disease, renal disease, asthma, failure to thrive, cystic fibrosis were excluded.⁶ Sixty patients were initially selected however eight patients who were initially included were excluded due to lack of follow up or due to a rise of another illness. Fifty-two participants were randomly assigned to a control or interventional group. Twenty-six participants received a probiotic (LGG 1×10^{10}) twice per day for four weeks. Twenty-six participants received a placebo (inulin) twice per day for four weeks. Patients were evaluated weekly with using the five-point likert scale to specify severity of pain. Although no significant difference was obtained regarding the baseline pain severity scales between the two groups, a statistically difference was observed from one week after treatment.⁶ The p-value one week after treatment was <0.01 . Data was continuous and not convertible to a dichotomous format. Outcomes were measured before intervention and weekly for four weeks in each group. Wilcoxon rank-sum test was used to compare changes in abdominal pain (Table 4).

Table 4: Pain severity before intervention and weekly for 4 weeks.

	Pre-treatment	1 week after Treatment	2 weeks after treatment	3 weeks after treatment	4 weeks after treatment
Probiotic	2.5 ± 0.9	1.5±1.0	1.2±1.1	1.0±0.9	0.8±0.9
Inulin (Placebo)	2.7±0.8	1.8±0.6	1.9±0.8	1.8±0.6	1.5±0.8
P-value	0.4	0.01	0.00	0.00	0.00

In the Jadresin et al study, the inclusion criteria were children between age 4 and 18 years old who had been diagnosed with IBS at the Children's Hospital Zagreb from May 2012 to December 2014.¹ Patients who had a known or suspected immunodeficiency, treated with probiotics and/or prebiotics seven days prior to enrollment, known neoplastic disorder, or any other chronic disease were excluded.¹ Written informed consent was obtained from the parent or guardian of each child in the study as well as from children if older than nine years.¹ Once patients were randomized, they were asked to report back to the hospital monthly.¹ Intervention lasted twelve weeks and patients were followed four weeks after intervention.¹ Children who were non-compliant to treatment were excluded.¹ Data was analyzed for fifty-five participants, twenty-six received a probiotic (450mg *L. reuteri* 1x10⁸) daily and twenty-nine received a placebo daily. There was a difference between both groups in the number of days without pain, with the median of 89.5 (range 5-108) days in the experimental group and 51 (range 0-107) days in the placebo group (p=0.029).¹ Participants taking the probiotic or inulin experienced significant reduction in severity of abdominal pain from first to fourth month, although reduction was more prominent in the experimental (probiotic) group (p<0.001 vs p=0.004) (table 5).¹ No adverse effects were reported. There was no significant differences in number of participants with complete resolution of abdominal pain between probiotic and inulin group.¹ Complete

resolution of abdominal pain until the end of treatment (16 weeks) was seen in 16 (61.5%) participants from active group and 16 (55.2%) participants from placebo group (p=0.633) (table 6).¹ All patients, including the patients who discontinued the intervention, were followed up until the end of the study; they were included into intention to treat analysis.¹ Data demonstrated relative benefit increase of 0.11% and absolute benefit increase 6.3%. NNT was 16. For every 16 children treated with probiotics it would prevent one fewer child from suffering abdominal discomfort, compared to the control group.

Table 5: Comparing severity of pain between beginning and end of treatment.

	Severity of abdominal pain per day in 1 st month, median (range)	Severity of abdominal pain per day in 4 th month, median (range)	P
Probiotics (active)	0.75 (0-2.9)	0.21 (0-1.7)	<0.001
Inulin (placebo)	0.96 (0.3-2.8)	0.6 (0-2)	0.004

Assessed by Wong-Baker FACES Pain Rating Scale per group (Wilcoxon test)

Table 6: Efficacy of Jadresin et al study

Resolution of abdominal pain abdominal pain in the control group (placebo) (CER)	Resolution of abdominal pain in the experiment group (probiotics) (EER)	Relative benefit Increase (RBI)	Absolute benefit Increase (ABI)	Numbers needed to treat (NNT)
55.2%	61.5%	0.11%	6.3%	16

Safe and Tolerability

In all three-randomized control trials no adverse events were reported in neither group. Probiotics were well tolerated. Patients experiencing active IBS symptoms such as constipation, diarrhea, or bloating probiotics did not aggregate or increase reoccurrence of IBS symptoms.

DISCUSSION

Irritable bowel syndrome is a condition that presents with various signs and symptoms. The main cause of IBS is inconclusive; however, it is recognized to be multifactorial. The

approach to managing irritable bowel syndrome is reducing the reoccurrence of gastrointestinal pain and discomfort. Non-pharmaceutical and pharmaceutical therapies may be implemented such as change in diet, exercising, counseling, medications.

Studies have been performed to determine the effectiveness of using probiotics to treat IBS but in the adult population. It is challenging to conduct trials in the pediatric population because there are more regulations such as receiving approval of the participants guardian. In the pediatric population, few studies have been done and results are inconclusive. Kianifar et al study, faced some limitations such as small sample size, short duration of treatment, and not following up after cessation of treatment.⁶ Basturk et al study found probiotics effective in children who have been diagnosed with IBS.⁷ However, a major limitation in the study was that it was done in a tertiary health care center which meant dealing with relatively more complex participants.⁷ Jadresin et al-study consisted of a small sample size. In future studies, long-term treatment and long-term follow up can help evaluate the efficiency of probiotics. It is suggested to conduct studies that include a large sample size, exclude patients who don't have a history of an underlying disease, and involve children from the general population to increase generalizability.

CONCLUSION

Based on these three studies, probiotics can treat abdominal pain in children between the ages of 4 & 18 with Irritable bowel syndrome. However, future research is warranted. Some ideas to consider is involving children from general population to increase generalizability, have a larger sample size, extend duration of study, and following up after cessation of treatment. Other items to consider is determining if combination therapy is more effective than monotherapy.

In the pediatric population, probiotics are being used to treat IBS. However, there has not been significant research to prove that it has been effective.

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