Wageningen Academic Publishers

Efficacy of *Bacillus coagulans* Unique IS2 in treatment of irritable bowel syndrome in children: a double blind, randomised placebo controlled study

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Received: 31 August 2017 / Accepted: 4 January 2018

RESEARCH ARTICLE

Abstract

The efficacy of the probiotic strain, *Bacillus coagulans* Unique IS2 in the treatment of Irritable Bowel Syndrome (IBS) was evaluated in children. A total of 141 children of either sex in the age group 4-12 years, diagnosed with IBS according to the Rome III criteria, participated in the double-blind randomised controlled trial. Children received either *B. coagulans* Unique IS2 chewable tablets or placebo once daily for eight weeks followed by a two week follow-up period. Reduction in pain intensity as well as other symptoms associated with Irritable Bowel Syndrome like abdominal discomfort, bloating, distension, sense of incomplete evacuation, straining at stool, urgency of bowel movement, passage of gas and mucus, and bowel habit satisfaction were assessed. *B. coagulans* Unique IS2 treated group showed a greater reduction in pain scores as evaluated by a weekly pain intensity scale. There was a significant reduction (P<0.0001) in pain intensity in the probiotic treated group (7.6±0.98) as compared to the placebo group (4.2±1.41) by the end of the treatment period (8 weeks). There was also a significant improvement in stool consistency as well as reduction in abdominal discomfort, bloating, staining, urgency, incomplete evacuation and passage of gas. Bowel habit satisfaction and global assessment of relief was also observed in the *B. coagulans* Unique IS2 treated group as compared to the placebo group. This study demonstrates the efficacy of *B. coagulans* Unique IS2 in reducing the symptoms of Irritable Bowel Syndrome in children in the age group of 4-12 years.

Keywords: *B. coagulans* Unique IS2, irritable bowel syndrome, probiotics

1. Introduction

Irritable Bowel Syndrome (IBS) is a chronic functional disorder of the gastrointestinal system of multifactorial aetiology characterised by frequent and unexplained symptoms that include abdominal pain, bloating and bowel disturbance (Canavan *et al.*, 2014). Patients experience altered bowel habit, with either predominantly diarrhoea (IBS-D), constipation (IBS-C) or both (IBS-M). IBS occurs in all age groups, including children and the elderly (Rasquin *et al.*, 2006; Tang *et al.*, 2012).

Studies have estimated the prevalence of IBS to range between 6-14% in children and between 22.0-35.5% in adolescents (Caplan *et al.*, 2005; Hyams *et al.*, 1996; Karabulut *et al.*, 2013; Miele *et al.*, 2004). IBS is one of the most common causes of recurrent abdominal pain in the paediatric population (El-Matary *et al.*, 2004). It affects the quality of life and requires management. There is no known single cause of IBS and it is believed to be multifactorial. Management of symptoms of irritable bowel syndrome can be challenging and may significantly impact the patient's quality of life (Jurenka, 2012). Therapeutic options for IBS are limited owing to the multitude of factors involved in the aetiology of IBS, its complexity and the side effects associated with usage of the drugs.

The gut microbiota is increasingly being recognised as playing a pivotal role in keeping the digestive system healthy and in maintaining eubiosis or the proper balance

of the intestinal flora. It is when the balance tilts leading to dysbiosis that most digestive disorders, including IBS, are known to occur (Collins, 2014).

IBS sometimes develops following recovery from enteric infections (Sekirov *et al.*, 2010; Spiller and Garsed, 2009), suggesting that infection-mediated disturbance in the host's gut microbial community results in gastrointestinal tract malfunction. Post-infectious IBS in animal models can be ameliorated with the administration of probiotic bacteria, which normalise muscle hypercontractility (Lutgendorff *et al.*, 2008), offering further evidence that post-infection microbiota disturbance contributes to IBS pathophysiology.

Many studies have suggested that probiotics are useful in the treatment of IBS through alterations in the gut bacteria. In a systematic review (Moayyedi *et al.*, 2010) on the efficacy of probiotics in the treatment of IBS, the conclusion drawn was that probiotics were efficacious in IBS, but the magnitude of benefit and the most effective species and strain were uncertain and needed to be ascertained.

There have been a few studies on the efficacy of *B. coagulans* in ameliorating the symptoms of IBS (Dolin, 2009; Hun, 2009). These studies have all been conducted in adults. Moreover, the effects of probiotics are strain specific. It was hence of interest to study the efficacy of the strain *B. coagulans* Unique IS2 on IBS symptoms in children. The present study conducted in children between ages 4-12 years indicates that *B. coagulans* Unique IS2 ameliorates the symptoms of IBS and improves quality of life.

2. Materials and methods

Study design

This double blind, randomised, placebo-controlled, parallel group multicentric study was conducted at the Angel Healthcare Paediatric outpatient clinic and Life Veda Treatment and Research Centre in Mumbai, India between February 2014 and October 2016. This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and Good Clinical Practice Guidelines as laid down by the Indian Council of Medical Research (ICMR). The informed consent forms were approved by ISBEC (Inter System Biomedica Ethics Committee) and the trial was registered with the Clinical Trial Registry – India (CTRI Reg No: CTRI/2017/02/007810). The double blind, randomised, placebo-controlled parallel group study was initiated after obtaining informed consent.

Study population

A total of 216 patients were screened, 62 were deemed as screening failures. The total number of patients enrolled was 154 with 141 patients completing the study (per protocol population). Thirteen were drop-outs or protocol deviations (Figure 1). Of the 141 patients completing the study, 72 patients received Treatment A (probiotic – *B. coagulans* Unique IS2 chewable tablets) and 69 patients received Treatment B (placebo chewable tablets) The mean age of the subjects in the per protocol population was 7.9 years. 61 (43.26%) patients were female and 80 (56.74%) were male. All subjects in the study were of Indian origin (Table 1).

Prohibited medicines included dietary fibre, bulking agents, laxatives, antispasmodic agents, antibiotics, antidiarrheals, probiotics, antidepressants and psychological and herbal therapies in the management of irritable bowel syndrome. Table 2 provides the list of other prohibited drugs.

Selection criteria

Inclusion criteria were patients of either sex between 4-12 years of age. All enrolled patients were diagnosed with IBS as defined by Rome III criteria:

1. Patients with abdominal discomfort or pain associated with two or more of the following at least 25% of the time:
   - improvement with defaecation;
   - onset associated with a change in frequency of stool;
   - onset associated with a change in the form (appearance) of stool.
2. There were no structural or metabolic abnormalities to explain the symptoms.

Patients having any of the following symptoms were included in the study: abnormal stool frequency defined as greater than 3 bowel movements per day or less than 3 bowel movements per week; abnormal stool form (lumpy/hard or loose/watery); abnormal stool passage (straining, urgency or feeling of incomplete evacuation); passage of mucus with stool and bloating or abdominal distension.

Exclusion criteria included patients diagnosed with other diseases affecting bowel motility other than IBS. Those with a history of lactose intolerance and other malabsorption syndromes (e.g. fructose malabsorption), previous abdominal surgery and patients suffering from severe systemic disease were also excluded. Other exclusion criteria included those who had been using commercial preparation of probiotics in the last three months, history of digestive disease (Crohn's, ulcerative colitis, oesophagitis, peptic ulcer, coeliac disease) or symptoms suggestive of rectal bleeding, and weight loss over 3 kg in the last three months as well as acute gastroenteritis in the last four weeks prior to inclusion. Children were screened for coeliac disease

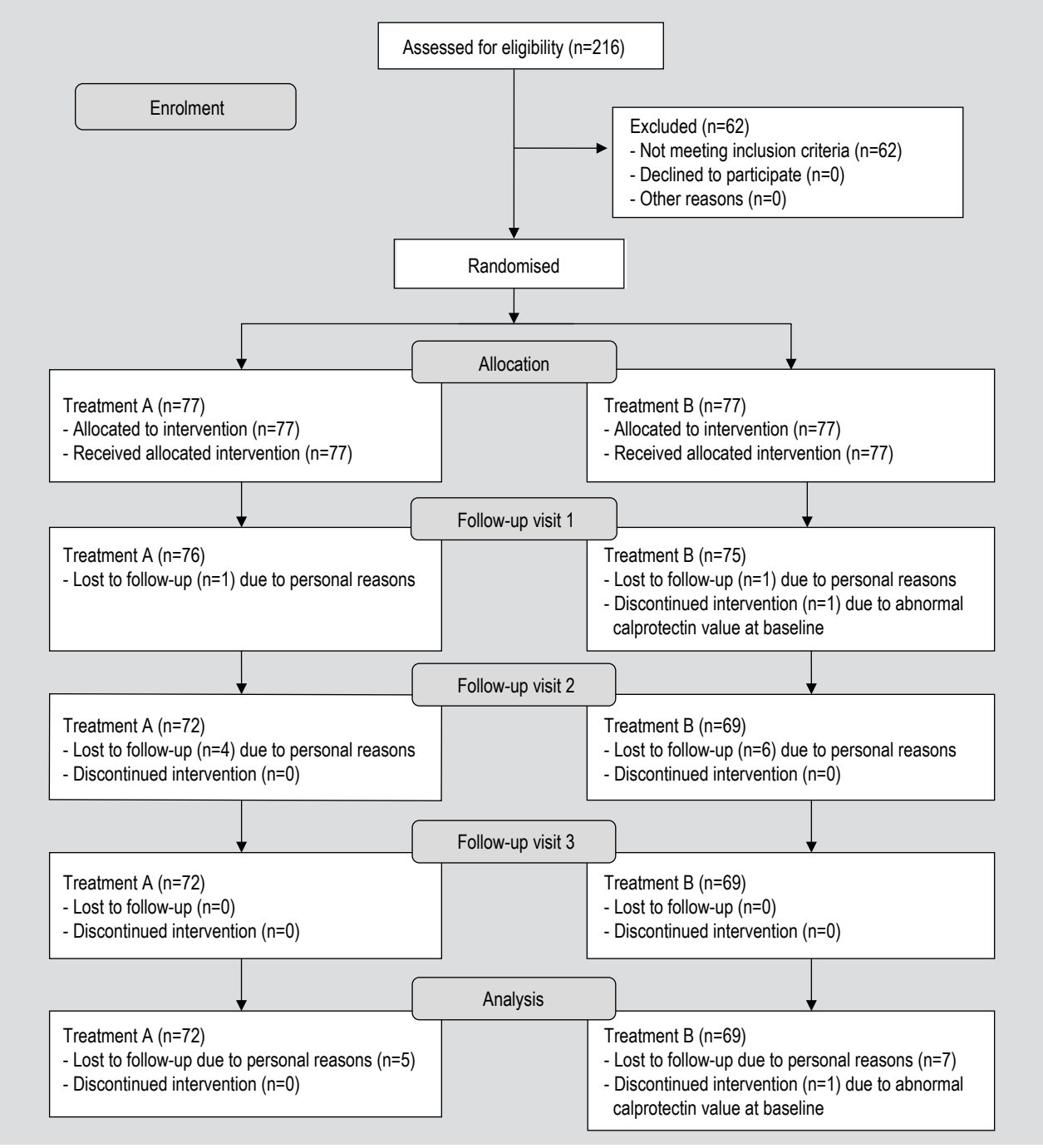

Figure 1. Study flow-chart.

by obtaining the medical history of the child and detailed family history. According to Balamtekın (2012), increased faecal calprotectin levels can be used as a non-invasive marker that might aid in the diagnosis of coeliac disease, especially in patients with gastrointestinal presentation. In our study calprotectin assay was conducted at baseline and patients having calprotectin assay of ≥500 µg/g stool were excluded from the study.

Randomisation

Patients complying with the selection criteria were enrolled in the study. Based on SAS version 9.4 (Cary, NC, USA), randomisation numbers for two treatment groups were generated. Randomisation was conducted using opaque sealed envelopes that were indistinguishable between groups in order for the investigators also to be blinded to the treatment. Each envelope had the assignment of the patient (Treatment A or B) with 140 envelopes for each

Table 1. Patient baseline characteristics.[1]

	Treatment A (n=72)	Treatment B (n=69)	Total (n=141)	*P*-value[2]
Gender n (%)				
Male	43 (59.72%)	37 (53.62%)	80 (56.74%)	0.4649
Female	29 (40.28%)	32 (46.38%)	61 (43.26%)	0.4649
Irritable bowel syndrome (IBS) subtype by predominant bowel habit n (%)				
Diarrhoea (IBS-D)	29 (40.28%)	29 (42.03%)	58 (41.13%)	0.8327
Constipation (IBS-C)	38 (52.78%)	35 (50.73%)	73 (51.77%)	0.8073
Mixed (IBS-M)	5 (6.94%)	5 (7.24%)	10 (7.10%)	0.9443
Age (years)				
Mean	7.86	7.89	7.90	
Median (min, max)	8 (4, 11)	8 (4, 10)	8 (4, 11)	

[1] Treatment A = *Bacillus coagulans* Unique IS2; Treatment B = placebo.
[2] Chi-square test was used to determine *P*-value for the frequency; all the above *P*-values are statistically non-significant.

Table 2. List of prohibited drugs.[1]

Drug	Mechanism of action	Targeted disorder
Crofelemer	CFTR inhibitor	IBS-D
Linaclotide	Guanylate cyclase-c agonist	IBS-C
Arverapamil	Calcium channel blocker	IBS-D
Asimadoline	Kappa opioid agonist	IBS
Mitemcinal	Motilin receptor agonist	IBS-C
Ramosetron	5-HT3 antagonist	IBS-D
TD-5108	5-HT4 agonist	IBS-C
DDP-773	5-HT3 agonist	IBS-C
DDP-225	5-HT3 antagonist and NE reuptake inhibition	IBS-D
BMS-562086	Corticotropin-releasing hormone antagonist	IBS-D
GW876008	Corticotropin-releasing hormone antagonist	IBS
GTP-010	Glucagon-like peptide	IBS pain
AGN-203818	Alpha receptor agonist	IBS pain
GW-427,353 (Solabegron)	Beta-3 receptor agonist	IBS
Espindolol (AGI-011)	Beta receptor antagonist	IBS (all subtypes)
Dextofisopam	2,3 benzodiazepinereceptors	IBS-D and IBS-M

[1] IBS = irritable bowel syndrome; IBS-C = IBS with constipation; IBS-D = IBS with diarrhoea; IBS-M = mixed IBS; CFTR = cystic fibrosis transmembrane conductance regulator; 5-HT3/4 = serotonin receptors; NE = norepinephrine reuptake inhibitor; Beta-3 receptor agonist = β3 adrenoreceptor; Beta receptor antagonist = beta blockers.

group. The sealed envelopes were provided to the clinical site. The investigators assigned investigational products to patients based on the randomisation numbers.

Study follow-up visits and treatments

The study was designed to consist of three phases: washout period (2 weeks), treatment period (8 weeks) and observational period after withdrawal of treatment (2 weeks). The 2-week run in period or washout period was to establish and ascertain patient compliance. The probiotic or placebo tablets were administered for a period of 8 weeks which was the treatment period. During the treatment period, patients visited the investigator on week 4 and week 8. Two weeks after the end of treatment (8 weeks), a telephonic follow-up (week 10) was conducted to assess recurrence of any symptoms.

Participants were dispensed the investigational product consisting of either *B. coagulans* Unique IS2 chewable tablets

(2×10^9 cfu) or the placebo chewable tablets. The *B. coagulans* Unique IS2 chewable tablets contained the active ingredient *B. coagulans* Unique IS2 and inactive ingredients dextrose, mannitol, magnesium stearate, colloidal silicon dioxide and crospovidone. The placebo chewable tablets were identical to the *B. coagulans* Unique IS2 chewable tablets in looks and composition except that the active ingredient was missing in the placebo tablets. Participants were instructed to take one chewable tablet per day. The tablets were stored at room temperature in a cool and dry place. Viability of the probiotic in the *B. coagulans* Unique IS2 chewable tablets was assured till the end of shelf life. Stability studies conducted with the chewable tablets in stability chambers according to ICH (International Conference on Harmonisation) guidelines confirmed the viability of the product. The participants were instructed to continue with their regular diet.

Efficacy and safety measurement criteria

The intensity of pain was measured with an 11-point Likert scale, where 0 represents no improvement and 10 the highest improvement (0 = very much worse, 1 = much worse, 2 = worse, 3 = less worse, 4 = very less worse, 5 = same pain, 6 = very less better, 7 = less better, 8 = better, 9 = much better and 10 = very much better). For children aged less than 8 years, the parent/caretaker was instructed to fill the patient diary. For children aged between 8 and 12 years, the patient diary was filled by the child and if required they were assisted by the parent/caretaker. Secondary efficacy variables were measured as: (a) change in the severity of symptoms score which consisted of eight domains (abdominal discomfort, bloating, urgency, incomplete evacuation, straining, passage of gas, bowel habit satisfaction and overall assessment of IBS) with a Likert scale of 1-5; (b) stool consistency (relief in stool disturbances or trouble with bowel habits, which is 'either going more or less often than normal, diarrhoea or constipation, or having a different kind of stool, thin, hard, or soft and liquid' measured with the Bristol stool scale of 1-7 and recorded by the patients in the diary; (c) Subject's Global Assessment of Relief (SGARC), a globally accepted validated questionnaire (Müller-Lissner *et al.,* 2003), which includes the assessment of overall wellbeing, abdominal pain/discomfort and bowel function (Likert scale 0-4). Drug compliance, usage of rescue medications, and adverse events (AE), if any, were monitored throughout the study.

Statistical analysis

Primary efficacy analysis

Reduction in the intensity of abdominal pain was evaluated using Wilcoxon-Mann-Whitney test for two independent groups (*B. coagulans* Unique IS2 and placebo). NRS is a patient related outcome (PRO) measure based on Likert scale. It is not a tool or instrument but a categorical scale and therefore evaluated using the Mann-Whitney test for two independent groups. For 141 patients, the study is sufficiently powered at 0.88 (88%), rejecting the null hypothesis that there is no difference between the two treatments *B. coagulans* Unique IS2 and placebo in reduction in the intensity of abdominal pain.

Secondary efficacy variables

Differences between the groups in the severity symptom scores were measured with Mann-Whitney test and chi-square test. Stool consistency assessment was done based on a 7-point score according to the Bristol Stool Chart; Chi-square test was utilised to evaluate the difference between the two groups after 8 weeks of therapy. SGARC was evaluated by a two sampled t-test and chi-square test for the difference between the two groups after 8 weeks of treatment. Frequency (%) of AE and need for rescue medications were noted to evaluate the difference after 8 weeks of treatment.

3. Results

Primary efficacy endpoint: abdominal pain intensity

NRS for pain was evaluated at baseline, week 4, 8 and 10 (Figure 2). The mean NRS for pain in the probiotic treated group at baseline was 3.8±0.55 (mean ± standard deviation) and in the placebo group was 3.7±0.49. This was significantly increased at Visit 1 (week 4) with the probiotic group rating 6.0±0.94 and the placebo group 5.01±1.08

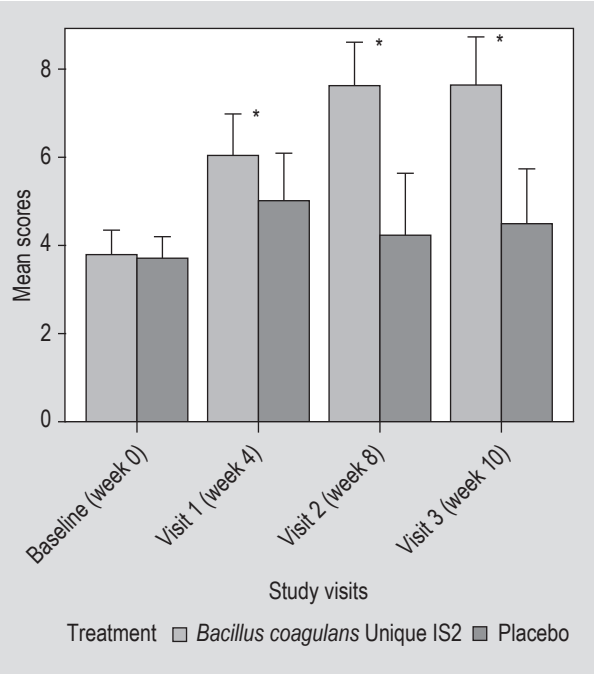

Figure 2. Effect of *Bacillus coagulans* Unique IS2 on abdominal pain intensity. Results are reported on a 0-10 Likert scale. Bars indicate standard deviation. * *P*<0.0001 between treatments.

(P<0.001). Similarly, during Visit 2 (week 8), the probiotic group scored 7.62±0.98 and the placebo group 4.23±1.40 (P<0.001). An increase in the numeric rating scale indicates a reduction of pain intensity.

Patients having >50% relief from the baseline visit were considered as responders in the study. Comparison after 4 weeks of treatment showed that in the probiotic group 59 patients out of 72 (81.94%) reported more than 50% relief from pain, whereas in the placebo group only 33 patients out of 69 (47.83%) reported 50% relief (chi-square test, P<0.001). Similarly, after 8 weeks of therapy in the probiotic group, 67 patients out of 72 (93.06%) were categorised as responders, whereas only 15 out of 69 (21.74%) patients were found to be responders in placebo group (chi-square test, P<0.001).

Secondary efficacy endpoints: severity symptom score analysis

The domain scores were found to be significantly reduced in the probiotic treated group compared to the placebo group, which indicated that the probiotic treated group showed improvement in the eight domain scores when compared from baseline to week 8. Mean ± standard deviation scores of abdominal discomfort at baseline were 3.4±0.70 and 3.6±0.67 and at week 8 were 0.5±0.82 and 2.4±1.19 for the probiotic and placebo group, respectively.

The symptom severity scores were compared between the treatment groups with a chi-square test at each week based on the PRO outcome. Significant improvement in the *B. coagulans* Unique IS2 treated group was observed from the fourth week onwards for symptoms like abdominal discomfort (P<0.0003), bloating (P<0.0005), urgency (P<0.0037), bowel habit satisfaction (P<0.0194) and total score (P<0.0030). Reduction in incomplete evacuation, straining, passage of gas and overall assessment of IBS symptoms were not significant at the fourth week. However, by the end of the fifth week, all the symptoms were significantly reduced (P<005 for straining, passage of gas P<0.0154, overall assessment of IBS P<0.001). These results (21.74%) indicated that at least four to five weeks of probiotic therapy was required for optimum reduction in disease severity. Table 3 shows the overall assessment of severity symptom scores.

Stool consistency analysis based on Bristol stool chart

A significant improvement in stool consistency was observed from the 6th week onwards of treatment (Figure 3), where almost 50% patients gained normal stool consistency, i.e. 38 patients out of 72 patients attained normal stool

Table 3. Summary of severity of symptoms score for each domain: baseline and final visit.

Domains	Visit	Treatment A (n=72)[1]		Treatment B (n=69)[1]		Absolute change from baseline			
		Mean	SD	Mean	SD	Mean	SD	*P*-value[2]	*P*-value[3]
Abdominal discomfort	baseline	3.4	0.70	3.6	0.67	0	0		
	week 8	0.5	0.82	2.4	1.19	-2.0	1.42	<0.0001	<0.0001
Bloating	baseline	3.0	0.92	3.1	0.91	0	0		
	week 8	0.6	0.78	2.2	0.91	-1.7	1.35	<0.0001	<0.0001
Urgency	baseline	3.1	0.73	3.1	0.71	0	0		
	week 8	0.9	0.81	1.9	1.00	-1.7	1.27	<0.0001	<0.0001
Incomplete evacuation	baseline	3.0	0.64	3.2	0.63	0	0		
	week 8	0.8	0.77	1.8	0.90	-1.8	1.17	0.0004	<0.0001
Straining	baseline	3.0	0.96	3.1	0.86	0	0		
	week 8	0.9	0.83	2.0	1.00	-1.6	1.37	0.0015	<0.0001
Passage of gas	baseline	3.4	0.69	3.3	0.56	0	0		
	week 8	0.8	0.80	1.9	1.00	-2.0	1.12	<0.0001	<0.0001
Bowel habit satisfaction	baseline	3.1	0.60	3.1	0.64	0	0		
	week 8	0.9	1.02	2.3	1.02	-1.5	1.43	<0.0001	<0.0001
Overall assessment of IBS	baseline	3.3	0.51	3.3	0.50	0	0		
	week 8	1.3	0.78	2.2	0.87	-1.5	1.05	<0.0001	<0.0001
Total score	baseline	25.2	3.16	25.6	2.82				
	week 8	6.7	4.43	16.9	5.53	-13.7	7.57	<0.0001	<0.0001

[1] Treatment A = *Bacillus coagulans* Unique IS2; Treatment B = placebo; n = number of patients; SD = standard deviation.

[2] Chi-square test.

[3] Wilcoxon-Mann-Whitney test for two independent groups.

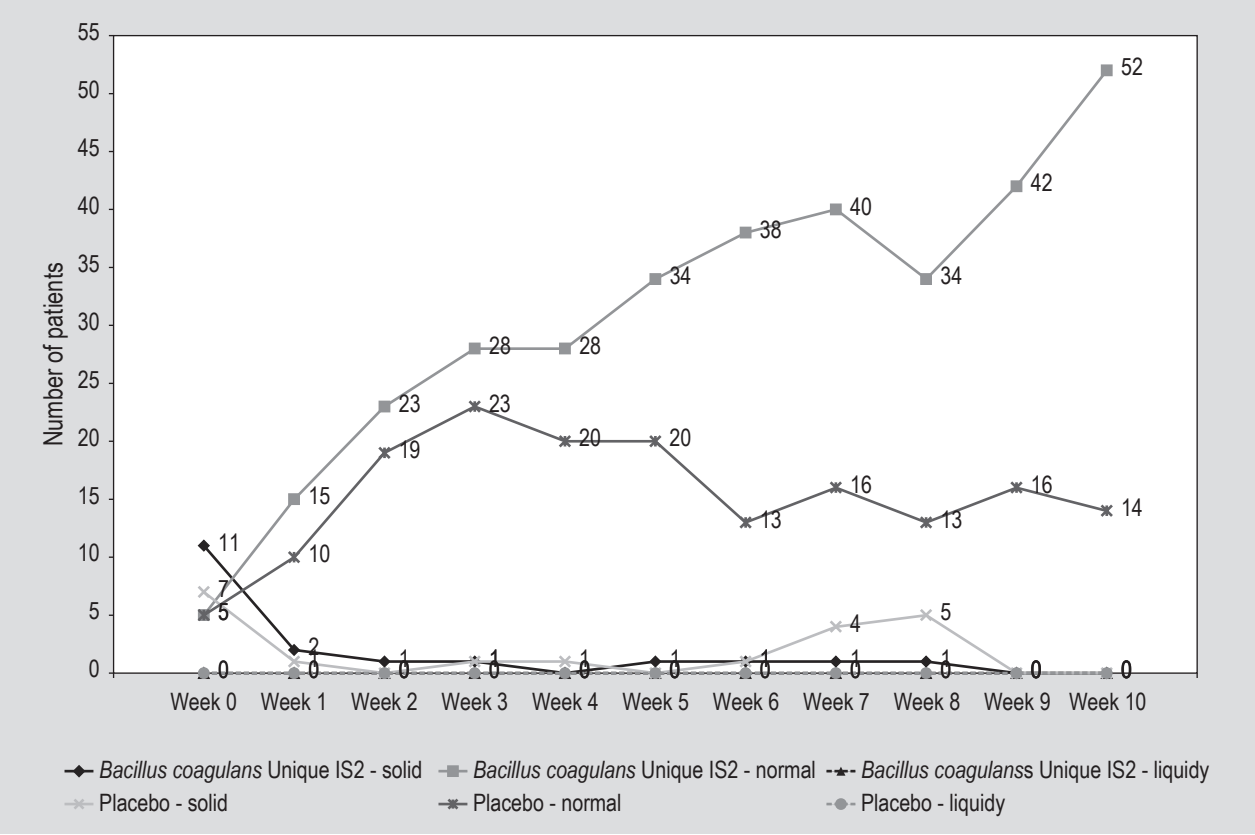

Figure 3. Effect of *Bacillus coagulans* Unique IS2 on stool consistency. Results indicate the number of patients transitioning to normal stool consistency over the treatment period.

consistency, whereas only 13 patients could return to normal stool consistency in the placebo group leading to a statistically significant difference ($P<0.0001$).

Subject's global assessment in relief of children

SGARC questionnaire was used to assess subject's global assessment in relief from IBS symptoms at week 0, 2, 4, 6, 8 and 10. SGARC questionnaire consisted of a total of five questions, each of which when evaluated from baseline to Week 8 for the probiotic treated group showed a reduction ($P<0.001$). There was thus a significant reduction in SGARC scores between the two-time points. The Mean SGARC total scores of the probiotic treated group was found to be significantly reduced at week 8 to 3.5±2.28 as compared to the placebo group (8.6±2.60). No relapse of symptoms was observed two weeks after discontinuation of probiotic treatment, assessed by a telephonic follow-up at week 10. The summary and trend of improvement in total score of SGARC is presented in Table 4 and Figure 4.

Rescue medication

There was no difference between the number of children who needed to use rescue medication in both the groups. Only 1-2 subjects in each group used the rescue medication.

Safety

A few AE in both groups, like cough, fever, fever with abdominal pain, fever and vomiting, flu like symptoms, gastritis, headache, nausea, nausea and vomiting, nausea and abdominal pain and vomiting were noted. None of the adverse events were related to the treatment. There was no significant difference noted between the two groups for the frequency of AE ($P=0.4168$). There were no serious AE in either group.

4. Discussion and conclusion

There are very few studies elucidating the efficacy of probiotics for the treatment of IBS in children. To the best of our knowledge, this is the first study conducted in children diagnosed with IBS on the efficacy of the probiotic strain, *B. coagulans* Unique IS2 in alleviating the symptoms of IBS. Sandhu and Paul (2014) have analysed studies conducted with probiotics in children diagnosed with IBS. In a study in Germany with 203 children (66 boys, 137 girls), aged 4 to 18 years (mean 10.5±4.5 years) treated with Symbioflor 2 (containing the natural intestinal bacterium *Escherichia coli*) for an average of 43 days, IBS symptoms (abdominal pain, stool frequency) as well as the other symptoms (bloating, mucus and blood in stool, need for straining at stools, urge

Table 4. Subject's Global Assessment of Relief (SGARC): baseline and final visit.[1]

SGARC questions	Visit	Treatment A (n=72)		Treatment B (n=69)		Absolute change from baseline			
		Mean	SD	Mean	SD	Mean	SD	*P*-value[2]	*P*-value[3]
How do you rate the relief of symptoms	baseline	3.2	0.60	3.3	0.57	-1.6	1.18	<0.0001	<0.0001
during the last week?	week 8	1.0	0.85	2.3	0.83				
Frequency and intensity of the	baseline	2.9	0.86	2.9	0.75	-1.6	1.19	<0.0001	<0.0001
abdominal pain/discomfort	week 8	0.8	0.76	1.8	0.70				
Abdominal bloating or gassiness	baseline	2.8	0.60	2.9	0.67	-1.6	0.97	<0.0001	<0.0001
	week 8	0.7	0.71	1.7	0.76				
Number and characteristics of the stools	baseline	2.5	0.53	2.4	0.55	-1.3	0.98	<0.0001	<0.0001
	week 8	0.7	0.68	1.6	0.86				
Family assessment of the impact of their	baseline	1.7	0.79	1.7	0.70	-0.9	1.05	0.0001	<0.0001
child's IBS on the family's life	week 8	0.3	0.50	1.3	0.74				
Total scores	baseline	13.1	1.64	13.2	1.56	-7.1	3.82	<0.0001	<0.0001
	week 8	3.5	2.28	8.6	2.60				

[1] Treatment A = *Bacillus coagulans* Unique IS2; Treatment B = placebo; n = number of patients; SD = standard deviation.
[2] Chi-square test.
[3] Two-sample *t*-test.

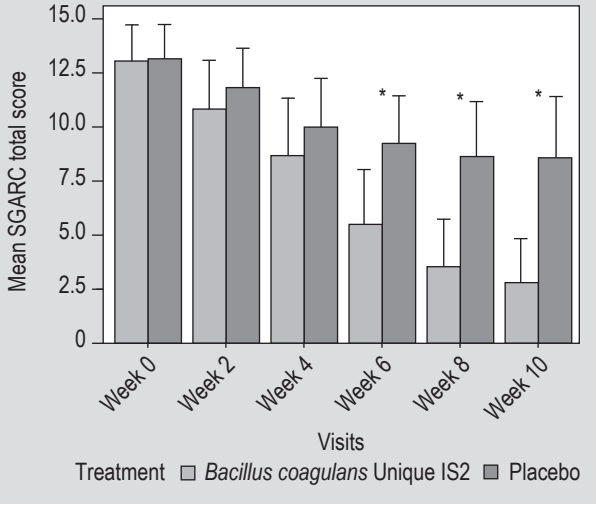

Figure 4. Effect of *Bacillus coagulans* Unique IS2 and placebo on total score of subjects global relief of symptoms (SGARC). Bars indicate standard deviation. * *P*<0.0001 between treatments.

to defaecate) improved significantly during treatment and the global assessment of therapy was found to be positive (Francavilla *et al.*, 2010). In a double-blind, placebo controlled, crossover trial conducted in 5 paediatric tertiary care centres (4 in Italy and 1 in India), 59 children (aged 4-18 years) were randomised to receive either VSL#3 or a placebo for 6 weeks. VSL#3 was found to be efficacious in both the primary (subjective assessment of relief of symptoms) and secondary endpoints (abdominal pain/discomfort, abdominal bloating/gassiness and family assessment of life disruption (Guandalini *et al.*, 2010). Another randomised double-blind, placebo controlled trial involved 141 children (aged 5-14 years) treated with *Lactobacillus rhamnosus* GG (LGG) or placebo for 8 weeks and then a further follow up for 8 weeks. When compared with baseline, children who received LGG reported a significant reduction in both frequency and severity of abdominal pain (Francavilla *et al.*, 2010).

Some of the mechanisms of action of probiotics in alleviating IBS include protection against pathogenic bacteria via their antimicrobial properties (Didari *et al.*, 2015; Gareau *et al.*, 2010) and amplification of the intestinal tight junctions to stabilise the permeability. Probiotics are also known to stimulate goblet cells to produce mucus to enhance the intestinal barrier function, normalise bowel movements and reduce visceral hypersensitivity (Gareau *et al.*, 2010) in both paediatric and adult patients (Enck *et al.*, 2011; Korterink *et al.*, 2014). Several probiotic strains have shown beneficial outcomes in IBS patients (Ortiz *et al.*, 2013; Whelan, 2011).

The efficacy of each probiotic strain has to be studied individually as probiotic effects are strain specific. *B. coagulans* Unique IS2, a very well documented, safe strain with a long shelf life and stability at room temperature, is the ideal candidate to be considered for IBS treatment in children. The advantages of *B. coagulans* Unique IS2 over other probiotic species, like lactobacilli, bifidobacteria and streptococci, is that it is a spore forming bacterium and

hence naturally encapsulated making it a highly resilient strain with superior viability even when stored at room temperature. Due to the formation of spores, *Bacillus* species have high heat and acid resistance. Most cells of ordinary lactobacilli die at 70 °C, while it has been reported that spore-bearing lactic acid forming bacteria do not show a decrease in viable cells even after heating in saline at 85 °C for 30 min and are also stable in artificial gastric juice (pH 2.0) for a typical time of application (3 h). Due to this property, relatively large numbers of spore-bearing lactic acid-forming bacteria can reach the large intestine unaffected by gastric acids and bile acids (Ara *et al.*, 2002).

The germination behaviour of *B. coagulans* Unique IS2 spores was studied in an *in vitro* model of the gastrointestinal tract – an adapted SHIME® (Prodigest's Simulator of the Human Intestinal Microbial Ecosystem) system representing the gastrointestinal tract of the adult human. Short-term colonic incubation experiments revealed that *B. coagulans* Unique IS2 spores germinated during the colonic incubations. The number of vegetative bacterial cells of this strain increased during the first 24 h of incubation indicating the active growth of the vegetative cells.

A preliminary study conducted in Iran (Saneian *et al.*, 2015) with *B. coagulans* Unique IS2 at a dose of 150×10^6 spores along with 100 mg fructooligosaccharides in children with functional abdominal pain, but not diagnosed with IBS, indicated a trend towards reduction of abdominal pain in the probiotic treated group during the treatment period. There was, however, no statistical significance between placebo and the probiotic treated groups after 8 weeks of treatment. The present study differs from it in that all patients were diagnosed with IBS and treatment was with the probiotic *B. coagulans* Unique IS2 alone at a dose of 2×10^9 cfu instead of the synbiotic combination with a much lower number of spores, which may have not been the effective dosage to establish efficacy.

B. coagulans Unique IS2 at a dose of 2×10^9 cfu/day was found to be efficacious in the treatment of IBS. Children receiving *B. coagulans* Unique IS2 chewable tablets showed significant improvement from the fifth week onwards in most of the features of IBS affecting quality of life. There was a significant decrease ($P<0.001$) in the intensity of pain (primary efficacy parameter) in the *B. coagulans* Unique IS2 treated group as compared to the placebo group.

The secondary efficacy parameters also showed a significant improvement for probiotic treated group as compared to placebo, i.e. in the eight domains of the severity symptom score (abdominal pain/discomfort, bloating/distension, sense of incomplete evacuation, straining at stool, urgency of bowel movement, passage of gas and mucus, and bowel habit satisfaction), and consistency of stools as reflected in the SGARC questionnaire. In conclusion, *B. coagulans* Unique IS2 exhibits tremendous potential as a therapeutic agent in IBS in children. The study suggests that it can reduce abdominal pain, discomfort, and disease severity and improve the stool consistency and quality of life for children and their families.

Conflict of interest

M. Ratna Sudha and N. Jayanthi are employed by Unique Biotech Ltd. which is a manufacturer of probiotics, including *B. coagulans* Unique IS2. They wish to state that the study was conducted independently through Integrity Health Services, Mumbai. The study was funded by Unique Biotech Ltd.

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