THE EFFECT OF MULTISTRAIN PROBIOTIC FORMULATION ON IRRITABLE BOWEL SYNDROME PATIENTS : A RANDOMIZED CONTROLLED CLINICAL TRIAL

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Summary

Probiotic formulation is useful in reducing symptoms of irritable bowel syndrome. To assess effectiveness of multistrain probiotics with standard treatment than standard treatment alone. This was a randomized control trial conducted in the Department of Gastroenterology, BSMMU, from July 2015 to June 2016. Patients with diagnosed case of IBS using Rome III criteria, absence of red flag sign like anemia, fever, weight loss, per rectal bleeding, nocturnal frequency, family history of IBD, cancer and age 18-55 years, no probiotics used in prior 3 months were included in the study. Patients were divided into group A (Standard treatment) and group B (Probiotics with standard treatment). Symptom severity scores especially for abdominal pain, global symptom severity were assessed at baseline, at one month interval during treatment for two months and one month post treatment. Mean age of the patients was 31.64 ± 9.72 years and 32.17 ± 10.03 years with no statistical significant difference with male female ratio of 4.2:1 and 3.06:1 in group A and group B respectively. Severity of abdominal pain, frequency of pain in every 10 days, severity of abdominal distension, satisfaction with bowel syndrome, frequency of open bowels per day gradually reduced in both groups but was higher in group B than group A (P<0.05). Passing mucus with motion was gradually reduced in both groups but the decrement was higher in group A than group B (p<0.05). Multistrain probiotics with standard treatment is more effective in reducing IBS symptoms than standard treatment alone.

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Irritable bowel syndrome; Probiotics; Intestinal motility

Introduction

Irritable Bowel Syndrome (IBS) is the most common functional GI disorder in clinical practice characterized by abdominal pain, bloating, change in stool frequency and consistency in the absence of an organic cause [1]. The worldwide prevalence is approximately 10-20% in adult affecting 14-24% of women, 5-15% of men in western countries [2]. If Rome III criteria is strongly used for diagnosis then 5-11% suffer from IBS, with similar prevalence in developed or developing countries [3]. It occur at any age (Peak in 30s - 40s) with female predominance [4]. IBS has a significant negative impact on quality of life and social functioning in many patients.

Its pathogenesis is multi factorial, altered intestinal motility, visceral hypersensitivity, abnormal brain gut interaction, food intolerance, altered intestinal permeability and post infectious changes. Recently, it has been emphasized alteration of gut micro flora through altered colonic fermentation produce symptoms - it increases gas formation, produce an abnormal pattern of short chain fatty acid resulting abnormal motility or sensitivity of the intestinal tract. Infectious gastroenteritis resulted in fourfold increase in the odds of developing IBS within subsequent 2 years diagnosis is dependent on symptoms and exclusion of major organic causes [5,6].

Spasmolytics, bulking agents, psychotropic agents, 5-HT receptor antagonists are used with disappointing result in relieving symptoms. Evidence has suggested significant reduction in abdominal pain; distension and flatulence, while increasing health-related quality of life in IBS using certain probiotics [7]. Probiotics are supplements containing live strains of beneficial bacteria ‘a live organism that, when ingested in adequate amounts, exerts a health benefit to the host’ [8].

Probiotics promote health by restoration of normal micro flora in the gut, increasing numbers of beneficial species, reducing numbers of pathogenic bacteria, increase trophic responses, regulate intestinal motility, modulate luminal immunity by changing cytokine and cellular milieu from a pro inflammatory to anti inflammatory state, regulate fermentation of non-degradable dietary fibre, intraluminal mucoproteins, favour lactose digestion, modulate intraluminal gas production [9]. Several studies with L. acidophilus, S. thermophilus, L.plantarum have shown improvement of bowel symptoms in IBS [10].

In Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka the result of a clinical trial to see efficacy of S. boulardii in diarrhea predominant IBS was not satisfactory, another study with multistrain probiotics yielded a beneficial outcome both clinically and statistically [11,12]. This study is aimed to assess the effectiveness of multistrain probiotics with standard treatment at reducing IBS symptoms than standard treatment alone and to see changes of quality of life before and after treatment.

Materials and methods

It was a prospective randomized controlled clinical trial conducted in the Department of Gastroenterology, BSMMU, Dhaka, Bangladesh from July 2015 to June 2016. Patients with diagnosed case of IBS using Rome III criteria, absence of red flag sign like anemia, fever, weight loss, per rectal bleeding, nocturnal frequency, family history of IBD, cancer, no probiotics used in prior 3 months, no prior use of antibiotic in last 2 months and age 18-55 years of both sexes were included in the study. Total 400 patients were recruited, finally 360 completed the trial. All were tested (FBC, ESR, CRP, Coeliac serology, blood sugar) to exclude other diagnosis and evaluated (Height,weight, BMI, psychological assessment-anxiety, depression) before intervention for baseline information. They were divided into group A (177 patients) and group B (183 patients) by randomization software. Patients in Group B received two capsules of probiotics (Bio-Kult, Sandoz BD Ltd.) twice daily before or during a meal (Equivalent to 8 billion CFUs) with standard treatment, while in group A received only standard treatment for eight weeks. Same dietary advice was given in two groups, anxiolytic and antidepressant were given in appropriate cases. Standard treatment was given according to symptom predominance, loperamide in diarrhea, ispaghula husk (10 gm daily) in constipation, mebeverine hydrochloride (135 mg, 8 hrly) for abdominal pain [13]. All were under follow up at one month interval during treatment for two months and one month post treatment.

Symptom severity scores especially for abdominal pain, global symptom severity were assessed at baseline and at each follow up by using a previously used validated IBS instrument [14]. This scoring was done on the basis of monthly interviews. The collective scores to these individual domains give rise to the total score. The IBS-SSS total score ranges from 0 to 500, a higher score indicating worse condition. Scores below 175 represent mild IBS, 175–300 represent moderate severity and scores above 300 represent severe IBS [15].Patients were asked to keep a diary with details of use of concomitant medication provided used consistently over last 2 months with a stable dose i.e. Loperamide or laxative including amount, frequency and duration. All data were recorded in a printed data sheet. Informed written consents were obtained from participants.

Statistical Analysis

Computer based statistical analysis were carried out with appropriate techniques and systems. All data were recorded systematically in preformed data collection form (Questionnaire) and quantitative data were expressed as mean and standard deviation and qualitative data were expressed as frequency distribution and percentage. Statistical analysis was performed by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-17) (SPSS Inc, Chicago, IL, USA). 95% confidence limit was taken. The summarized data was interpreted accordingly and was then presented in the form of tables. Categorical data were tested with Chi-square test and continuous data were tested with unpaired t-test.

Results

Among 400 enrolled patients of IBS, 360 patients completed the trial. Among them in group A 177 and in group B 183 patients. Minimum age was 18 yrs and maximum age was 55 yrs in both group. Most of the patients, 91 (51.4%) in group A and 62 (33.9%) in group B were between 21-30 yrs of age. Mean age in group A were 31.64 ± 9.72, in group B 32.17 ± 10.03. There was no statistically significant difference in age between two groups (p=0.661). In both groups, male patients were predominant (80.8 % in group A, 75.4% in group B). Male and female ratio was 4.2:1 in group A, 3.06:1 in group B. Most patients- 49 (27.7%) in group A and 60 (32.8%) in group B were service holder followed by students- 37 (20.9%) in group A and (28.4%) in group B respectively. In group A 30 (16.9%) worker, 25 (14.1%) housewife, 23 (13.0 %) businessman and in group B 22(12.0%) housewife, 19(10.4%) businessman and 16 (8.7%) worker suffered from IBS.

Severity of abdominal pain was assessed at base line and at each follow up in both groups and table I showed that pain improved with treatment in both groups but decrement of severity of abdominal pain was higher in group B than in group A which was statistically significant (p < .001).

Table I : Severity of abdominal pain of IBS patients before treatment and at different follow up after treatment in groups (n=360)

Severity of abdominal pain	Group A (n=177)	Group B (n=183)	Total (n=360)	p value
Before treatment	57.23 ± 10.59	58.44 ± 11.03	57.85 ± 10.82	0.289
At 1st month	36.85 ± 18.41	31.29 ± 13.88	34.02 ± 14.44	<0.001
At 2nd month	31.91 ± 18.41	24.60 ± 15.83	28.21 ± 17.52	<0.001
At 3rd month	34.42 ± 19.02	21.19 ± 15.50	27.73 ± 18.53	<0.001

Unpaired t-test

Frequency of pain was calculated by number of days patients experienced pain at every 10 days before treatment and after treatment at each follow up in both groups. Table II showed that with treatment pain frequency was reduced in both groups but reduction of frequency of pain was higher in group B than group A which was statistically significant (p < 0.001).

Table II : Number of days get pain in every 10 days before treatment and after treatment in groups (n=360)

Number of days get pain in every 10 days	Group A	Group B (n=177)	Total (n=183)	p value (n=360)
Before treatment	8.14 ± 2.27	7.62 ± 2.26	7.88 ± 2.28	0.033
At 1st month	4.62 ± 2.41	3.70 ± 2.07	4.15 ± 2.29	<0.001
At 2nd month	3.88 ± 2.62	3.02 ± 2.23	3.45 ± 2.47	<0.001
At 3rd month	4.35 ± 2.77	2.61 ± 2.17	3.47 ± 2.63	<0.001

Unpaired t-test

Feeling of abdominal distension was assessed at base line and after treatment in both groups at each follow up. Table III showed severity of abdominal distension gradually reduced in both groups but was higher in group B than group A which was statistically significant (p <.001).

Table III : Severity of abdominal distension before treatment and at different follow up after treatment in groups (n=360)

Severity of abdominal distension	Group A (n=177)	Group B (n=183)	Total (n=360)	p value
Before treatment	58.98 ± 12.03	58.42 ± 11.48	58.69 ± 11.74	0.647
At 1st month	42.05 ± 16.08	35.71 ± 14.75	38.76 ± 15.70	<0.001
At 2nd month	38.57 ± 18.28	27.12 ± 16.13	32.69 ± 18.11	<0.001
At 3rd month	38.58 ± 21.86	22.56 ± 15.85	30.62 ± 20.70	<0.001

Unpaired t-test

Satisfaction with bowel syndrome was assessed with treatment in both groups (table IV) and satisfaction score gradually reduced in both groups but it statistically significantly reduced in group B than group A (p < .001).

Table IV : Satisfaction with bowel syndrome before treatment and at different follow up after treatment in groups (n=360)

Satisfaction with bowel syndrome	Group A (n=177)	Group B (n=183)	Total (n=360)	p value
Before treatment	69.69 ± 13.11	70.90 ± 9.80	70.31 ± 11.55	0.320
At 1st month	50.49 ± 16.82	45.19 ± 13.43	47.81 ± 15.41	<0.001
At 2nd month	43.74 ± 19.13	34.56 ± 16.85	39.07 ± 18.56	<0.001
At 3rd month	46.34 ± 21.99	29.81 ± 18.06	37.94 ± 21.70	<0.001

Unpaired t-test

Reduction of frequency of open bowels per day was assessed at baseline and at each follow up (Table V) which showed statistically significantly higher reduction in group B than group A (p < .001).

Table V : Highest no. of times open bowels/day before treatment and at different follow up after treatment in groups (n=360)

Highest no. of times open bowels/day	Group			
	Group A (n=177)	Group B (n=183)	Total (n=360)	p value
Before treatment	5.57 ± 1.75	6.07 ± 2.58	5.83 ± 2.23	0.033
At 1st month	3.35 ± 1.40	3.30 ± 1.40	3.33 ± 1.40	0.737
At 2nd month	3.20 ± 1.32	2.91 ± 1.16	3.06 ± 1.25	0.027
At 3rd month	3.61 ± 1.30	2.96 ± 1.51	3.28 ± 1.44	<0.001

Unpaired t-test

Reduction of passage of mucus with motion was also assessed (table VI) which was higher in group A than group B (p = 0.167).

Table VI : Passing mucus with motion before treatment and at different follow ups after treatment (n=360)

Passing mucus with motion	Group			
	Group A (n=177)	Group B (n=183)	Total (n=360)	p value
Before treatment	177 (100.0)	183 (100.0)	360 (100.0)	
At 1st month	175 (98.9)	172 (94.0)	347 (96.4)	0.013
At 2nd month	173 (97.7)	178 (97.3)	351 (97.5)	0.774
At 3rd month	175 (98.9)	177 (96.7)	352 (97.8)	0.167

Unpaired t-test.

Discussion

Irritable Bowel Syndrome (IBS) is a common complaint observed in clinical practice and is characterized by abdominal pain, feeling of excessive gas and altered bowel habit in the absence of any structural, inflammatory or biochemical abnormalities [16]. IBS affects approximately 15% of the general population and is also observed in children [17].

IBS is a chronic, recurring disease, which although not fatal, it affects the quality of patients' lives by mandating frequent medical attention and increased job absences [18]. Therefore, in most cases, some form of treatment should be offered to patients. The pathogenesis of IBS is not well understood. Etiologies that include altered gastrointestinal motility, visceral hyperalgesia, stress, altered intraluminal microflora and immune system activation have been proposed [19].

Intestinal microbiota are important against carcinogens, for vitamin production and bile acid degradation, in addition to barriers against pathogens. Additionally, intestinal microbiota have a pivotal role in immune system development and function.

The increased risk of IBS after gastroenteritis is well recognized and suggests a possible role of change in microflora and activation of immune pathways in its pathogenesis [20]. Significant reduction in Lactobacillus and Bifidobacterium levels in IBS patients has been reported [21]. Current medications for IBS are generally unsatisfactory. Considering the current knowledge regarding gut flora and its alteration in IBS patients, manipulating the microbiota has been proposed as a plausible way to control IBS [22]. Probiotics are live organisms such as Lactobacilli and Bifidobacteria which are believed to be of benefit to the health of the host when ingested in adequate amounts [23]. There are several studies on the effects of probiotics in IBS patients with variable and conflicting results.

There is a growing interest in the relationship between gut microbiota and human health and disease [24]. Alterations in intestinal microbiota employing probiotics, prebiotics, synbiotics and antibiotics are used in attempts to treat gastrointestinal disorders including IBS [25]. Probiotics are effective in the treatment of IBS symptoms, but the most effective species are unclear [26]. This randomized controlled clinical trial was conducted at the Department of Gastroentarolgy, BSMMU, Dhaka during July 2015 to June 2016 for a period of one year to see the changes in abdominal pain and overall symptom severity of IBS patients.

A total number of 400 IBS patients were recruited. Finally 360 patients completed the study of which 177 patients were in group A and 183 patients were in group B. The distribution of IBS patients according to age in study and control group was recorded. Mean age of the patients were 31.64±9.72 years and 32.17±10.03 years in group A and group B respectively. There was no statistical significance between these groups. In this study it has been found that middle age group of people are most commonly affected by IBS patients which is consistent with another study where it was also found middle age group of people are mostly affected by IBS [18]. Another study has reported that children are also affected by IBS [17].

The distribution of IBS patients according to gender in study and control group were recorded. Male were predominant in both groups. Male and female ratio was 4.2:1 and 3.06:1 in group A and group B respectively. In another study it has been reported that IBS affects approximately 15% of the general population and has a female predominance [17].

The distribution of IBS patients according to occupation was recorded. In group A, service holder (27.7%) were maximum followed by Student (20.9%), Worker (16.9%) Housewife (14.1%) Businessperson (13.0%) and so on. In group B, service holder (32.8%) was the maximum followed by Student (28.4%) Housewife (12.0%) Businessperson (10.4%) Worker (8.7%) and so on. From this result it is very clear that the service holder are most commonly affected by IBS. The probable reason may be due to mental stress related to the service triggers the IBS problems.

Several approaches employed to treat the IBS cases of which pharmacologic, psychologic, and complementary approaches are mostly considered as therapeutic options in IBS patients [27]. Pharmacologic medications include antispasmodics, selective serotonin reuptake inhibitors, tricyclic antidepressants and 5-hydroxytryptamine type-3 antagonists such as ramosetron, alosetron, lubiprostone and linaclotide [28]. However, due to lack of favorable efficacy and associated adverse events with pharmacologic treatments, some IBS patients look for alternative treatments such as herbal medications and Chinese acupuncture [29,30]. Probiotics are live microorganisms which have been demonstrated to exhibit potential effects on human health [31]. Probiotics may influence the IBS symptoms including abdominal pain, bloating, distension, flatulence, altered bowel movements, and gut microbiota [32,33].

In this study the severity of abdominal pain of IBS patients before treatment and at different follow ups after treatment were recorded. Severity of abdominal pain according VAS gradually reduced in both groups after treatment but the decrement was higher in group B than group A. Furthermore, the frequency of pain in every 10 days of IBS patients before treatment and at different follow ups after treatment was recorded. Where it is observed that pain in every 10 days gradually reduced in both groups; however, the decrement was higher in group B than group A. Which is quite consistent with another study where it was reported that probiotics significantly reduce pain severity after eight and ten weeks of administration [34]. However, the reduction rate was rather higher at week eight than week ten, suggesting reduced effectiveness with long-term use [35]. It has been reported that the responder rate based on abdominal pain was significantly more than placebo which is consistent with the present study [36]. Another small study of 40 patients with IBS showed that treatment with L. acidophilus for four weeks was superior to placebo in decreasing abdominal pain [37]. But in contrast to the present study result it has been reported that probiotics exert no beneficial effect on abdominal pain which is dissimilar to the present study findings [38,39].

The severity of abdominal distension of IBS patients before treatment and at different follow ups after treatment was recorded. Severity of abdominal distension gradually reduced in both groups but the decrement was higher in group B than group A. In another study abdominal distension was evaluated by an IBS severity scoring system in three trials from two studies to compare the effect of probiotics therapy with placebo in IBS patients and have found similar result [40].

The satisfaction with alteration of bowel habit of IBS patients before treatment and at different follow ups after treatment was recorded. Severity score related to symptoms to the satisfaction of alteration of bowel habit gradually reduced in both groups but the decrement was higher in group B than group A. Here higher the score lower the satisfaction and vice versa. This is consistent with another study result which showed satisfaction of reduction of bowel syndrome was remarkably improved by using probiotics [34].

The frequency of bowel movement per day of IBS patients before treatment and at different follow ups after treatment was recorded. Frequency of bowel movement per day gradually reduced in both groups but the decrement was higher in group B than group A. The passing of mucus with stool of IBS patients before treatment and at different follow ups after treatment were recorded.

Passing of mucus with stool were gradually reduced in both groups but the decrement was more in group A than group B. Another similar study found that probiotics stimulate goblet cells to produce mucus to enhance the intestinal barrier function, normalize bowel movements, and reduce visceral hypersensitivity in pediatric and adult patients [41]. Although probiotic organisms exert beneficial effects to the host, they can act as a double-edged sword with both negative and positive effects. Therefore, precaution is necessary before they are administered [42]. The responder rate was significantly higher in probiotics-treated groups when global symptom improvement was considered [36,43]. Probiotics were effective in inducing an adequate improvement of general IBS symptoms [36,44,45]. The nature of probiotics explains their beneficial role in intestinal function as they can protect against pathogenic bacteria via their antimicrobial properties [46]. Probiotics also amplify the intestinal tight junctions and stabilize the permeability. Several probiotic strains showed beneficial outcomes in IBS patients [47]. The composition of gut microbiota in patients with IBS is different to that in healthy people and this fact underpins the use of probiotics in IBS treatment [37]. However, although treatment with multispecies probiotics rather than a single organism relieve some IBS symptoms, it is not clear which organisms induce the change in intestinal microbiota [26].

Limitation of the study

The study was done in a single referral center–The BSMMU hospital hence it is not representative of the whole population of the country.

Recommendations

Further nationwide multicentre study should be done to find out the effectiveness of multistrain probiotics in our population.

Conclusion

Combination of multistrain probiotics is more effective with standard treatment in reducing IBS symptoms than standard treatment alone in patient with IBS. The abdominal pain, abdominal distension and frequency of bowel movement per day of IBS patients are significantly reduced with multistrain probiotics treated patients.

Disclosure

All the authors declared no competing interest.

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