Original Article

A prospective, randomized, open-label, placebo-controlled comparative study of *Bacillus coagulans* GBI-30,6086 with digestive enzymes in improving indigestion in geriatric population

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Abstract

Introduction: Digestive symptoms are common affecting more than 60% of the elderly people. Digestive enzyme deficiency and dysbiosis in the gastric fluid microbiota are the major contributors in the pathophysiology of indigestion. Therefore, therapeutic strategy targeting the gastric microbiota and digestive enzymes has the potential to treat indigestion. This study was conducted to evaluate the efficacy and tolerability of probiotic *Bacillus coagulans* GBI30,6086 along with digestive enzymes in improving indigestion in geriatric population. **Methods:** An open-labelled, randomized, prospective study was conducted in geriatric patients with complaints of indigestion. The study group (n = 25) received 5 ml of reconstituted probiotic syrup containing *Bacillus coagulans* GBI-30, 6086, and digestive enzymes daily and the control group (n = 25) received 5 ml of placebo syrup twice daily for 5 days and followed-up after 7 days. **Results:** Reduction in Modified Glasgow dyspepsia severity score from baseline to follow up was statistically significant in the study group when compared to the control group ($P < 0.0001$). Improvement in indigestion, abdominal pain, and flatulence was also greater in the study group compared to the control group. **Conclusion:** *Bacillus coagulans* along with digestive enzymes are effective in treating indigestion in geriatric patients. It is well tolerated and safe to be used in geriatric patients without any major adverse effects.

Keywords: *Bacillus coagulans*, digestive enzymes, geriatrics, indigestion

Introduction

The study of gastrointestinal problems in elderly is a priority for primary care physicians as they constitute an ever increasing part of the population.[1] Over the years researchers have speculated that functioning of the gastrointestinal tract declines with aging. It was hypothesized that the efficiency of digestion and absorption declines with age which is now found to be true with rigorous testing.[2] Indigestion and its symptoms are associated with poor quality of life, increased absenteeism from work, and also constitute a significant burden on the health care system.

Indigestion is very common in the community, with prevalence of 30% and above.[3] Upto 40% of patients will consult a primary care physician as a result. From the primary care perspective, dyspepsia is a chronic condition of relapsing and remitting

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nature which may be vicious.[4] A community-based longitudinal follow-up study has reported 2% incidence of dyspepsia per year. In addition, a high prevalence of 40% of dyspepsia has been observed in this 10-year study indicating a very low cure rate of dyspepsia of 6% per year.[5] Though in the community dyspepsia was not associated with increase in mortality, due consideration has to be given to health care costs for treatment of dyspepsia.[6,7] Patients who do not fit into the alarming criteria for dyspepsia classified as uncomplicated dyspepsia need primary care management at the first instance.[8]

Common gastrointestinal complaints in elderly patients are indigestion, abdominal pain, flatulence, GERD which affects more than 60% of the elderly population.[3] These complaints have multiple triggers like changing food habits, processed food items, improper food timings, multiple medications, reduced production of digestive enzymes, recurrent abdominal infections, stress, etc.[9]

Although the pathophysiology of indigestion remains unclear, drastic reduction in digestive enzymes production, delayed gastric emptying, impaired gastric accommodation, and visceral hypersensitivity have been suggested as the underlying mechanisms.[10] A study by Nakae *et al.* found significant dysbiosis in the gastric fluid microbiota of patients with indigestion and considered it to be the underlying pathogenesis.[11] Therefore, an optimal balance between indigenous beneficial bacteria and potentially pathogenic bacteria in the gut is essential for efficient digestion and nutrient absorption. Also various digestive enzymes, amylase, protease, and lipases act as a biological catalyst in the process of digestion. Imbalances in this gastrointestinal milieu which occur due to aging can lead to indigestion and other symptoms like abdominal pain and flatulence.[12] Indigestion causes malabsorption of nutrients and in turn malnutrition and breakdown of immune system in elderly patients. Malnutrition is one of the most relevant conditions that negatively influence the health of older people. The nutritional status of elderly has been shown to predict preterm death.[13] Therefore, maintaining a good GI/digestive health is of paramount importance and is the key to overall good health.

Administration of probiotics will normalize the altered gastric fluid microbiota and seems to be the potential therapy in treating indigestion and its symptoms. However, there is limited literature available regarding probiotics as therapeutic option in the management of indigestion in elderly age group. Hence, this study was conducted to evaluate the efficacy and tolerability of probiotic *Bacillus coagulans* GBI 30, 6086 along with digestive enzymes in improving indigestion, reducing abdominal pain, and flatulence in geriatric population.

Materials and Methods

An open-labelled, randomized, prospective study was conducted in geriatric patients with complaints of indigestion attending Medical Gastroenterology OPD of Rajiv Gandhi Government General Hospital, Chennai. EC Reg No. ECR/270/Inst./TN/2013. The study drug is a probiotic supplement containing *Bacillus coagulans* as well as an enzyme blend of amylase, pepsin, and lipase (Tummy soft). Dry syrup of the study was reconstituted with freshly boiled and cooled water up to the arrow mark on the label and kept in refrigerator after reconstitution. The bottle was shaken well before use. It was given at a dose of 5 ml twice daily for 5 days.

Patient selection

A total of 50 subjects were randomized into interventional and control groups of 25 each. The inclusion criteria to participate in this study are as follows. Males and females between 55 and 75 years of age suffering from indigestion, abdominal pain, and flatulence with no significant upper gastrointestinal endoscopic findings and who are willing to give written informed consent were included in the study. Subjects with dysphagia, hematemesis, melena, abdominal tenderness, and abdominal mass, evidence of clinically significant renal, respiratory, hematological, endocrinological, neurological, psychiatric, or cardiovascular dysfunctions and severe malnourishment were excluded from the study. Also, patients who are smokers, alcoholics, with h/o intolerance/hypersensitivity to probiotics or h/o probiotic administration within past one month were excluded from the study.

Study procedure

Subjects were randomized into interventional and control groups of 25 each. The study was conducted after obtaining the approval from the Institutional Ethics Committee (Ethical committee approval number: ECR/270/INST./TN/2013, The date of approval is 07.11.2017), Madras Medical College. Patients were explained about the study purpose and procedures. Informed consent was obtained from the patients who were willing to participate in the trial. The demographic details of the patients' were recorded. Patients were screened by their history, general, and systemic examinations and laboratory investigations. Patients who fulfil the inclusion and exclusion criteria were enrolled and randomized to either the test group or control group. The study group (n = 25) patients received 5 ml of reconstituted probiotic syrup containing *Bacillus coagulans* GBI-30,6086 500 million CFU, alpha amylase 25 mg, pepsin 10 mg, and lipase 1.5 mg twice daily and the control group (n = 25) patients received 5 ml of placebo syrup twice daily for 5 days and followed-up after 7 days. During the study, the patients were asked to fill the Modified Version of the Glasgow Dyspepsia Questionnaire at first visit and also at the follow-up visit. Assessment of improvement Modified Glasgow Dyspepsia severity score from baseline to follow up visit.

Study endpoints

The primary endpoint of the study was to observe the difference in the score of Modified Glasgow Dyspepsia severity score from baseline to follow up. The secondary endpoints were improvement in indigestion 1 week after the end of therapy (day 12), reduction

in abdominal pain, and flatulence. Tolerability and safety were assessed based on the adverse effects as mentioned by patients and evaluated by the investigator.

Statistical analysis

Sample size was determined on the basis of time, cost, and the ability to detect a clinically important effect size. It was determined that 25 analyzable subjects per group would provide 80% power to obtain a significant result. Baseline characteristics like age, gender, and biochemical investigations were analyzed using student *t* test. Primary end points and secondary end points were analyzed using Fisher's test. Statistical analysis was done using SPSS.

Results

This study was carried out in 50 geriatric patients suffering from indigestion, of whom, 25 subjects were included in the study group and 25 subjects in the control group. The mean age of the study group was 64.2 ± 5.88 years and control group was 61.08 ± 5.83 years. The demographic characteristics (mean age, gender, random blood sugar, urea, and creatinine) are mentioned in Table 1. All the baseline characteristics were similar in both groups and with respect to age, gender, severity of the disease and lab findings and both the groups were comparable with no statistically significant difference between them. In both groups, the subjects presented with symptoms of indigestion, abdominal pain, and flatulence.

The assessment of severity of the symptoms was done using Modified version of the Glasgow dyspepsia severity score at baseline and 1 week after the end of the treatment Table 2. In the study group, the Modified Glasgow dyspepsia severity score reduced from 9.08 ± 1.706 at baseline to 4.16 ± 1.99 at 1 week after the end of therapy which was also statistically significant with *p*- <0.0001. In the control group, the score reduced from 8.84 ± 1.49 at baseline to 7.96 ± 1.54 at 1 weeks after the end of therapy which was also statistically significant with *P* value = 0.0445. Reduction in scores is higher in study group when compared to control group at follow up which is also statistically significant (*P* value < 0.0001) as mentioned in Table 2.

Figures 1 and 2 depicts Improvement in indigestion, abdominal pain and flatulence. Improvement in indigestion was seen in only 28% of the patients in the control group whereas 60% of the patients in study group showed improvement in indigestion which is statistically significant when compared to control group (*P* value = 0.045). Reduction in abdominal pain was seen only in 20% of the subjects in the control group whereas 56% of the patients had a reduction in the study group which is statistically significant with *P* value = 0.0186. In the control group, only 20% of the patients had improvement in flatulence, whereas 68% of the patients in the study group which is statistically highly significant with *P* value = 0.0015. All 50 subjects were evaluated for safety and tolerability. Eight subjects in the control group and six subjects in the study group complained of adverse drug reactions which included headache, nausea, vomiting, and myalgia as described in Table 3.

Table 1: Demographic details

		Control Group	Study group	*p*
No. of patients		25	25	
Mean age (years)		61.08±5.83	64.2±5.88	0.0656
SEX	Male	16	15	
	Female	9	10	0.7708
Random Blood Sugar		105.2±10.58	104.56±12.16	0.8243
Urea		29.6±4.74	30.56±2.97	0.3955
Creatinine		1.05±0.27	0.97±0.16	0.2301

Table 2: Modified version of the Glasgow dyspepsia severity score

	Control group	Study group	*p*
BASELINE	8.84±1.49	9.08±1.706	0.5992
FOLLOW UP	7.96±1.54	4.16±1.99	< 0.0001
P	0.0445 *	<0.0001 **	

*Significant, **Highly Significant

Table 3: Adverse drug reactions monitoring

ADR	Control group	Study group
HEADACHE	2	1
NAUSEA	3	2
VOMITING	1	1
MYALGIA	2	2

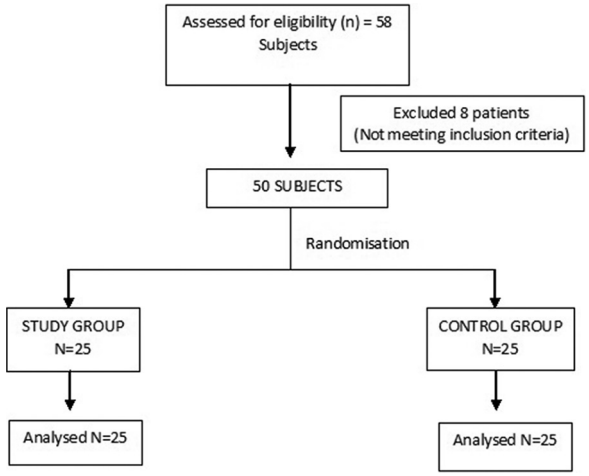

Figure 1: Consort flow diagram

Discussion

Digestive symptoms are common, affecting more than 60% of adults. Individuals with indigestion suffer significant morbidity and expend significant resources through both direct and indirect costs.[14] The common symptoms of indigestion include abdominal pain, a feeling of undue fullness after eating, loss of appetite, nausea, or vomiting and excessive. The gut microbiota of elderly subjects is characterized by a reduced bacterial diversity

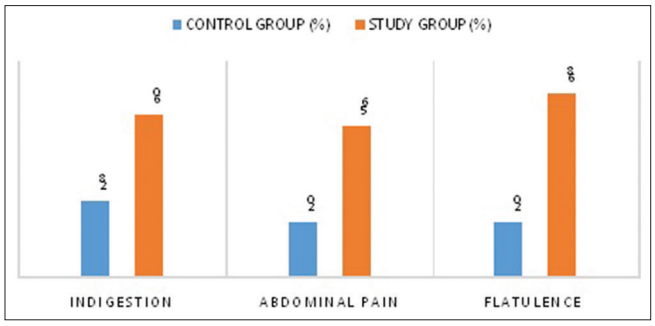

Figure 2: Improvement in indigestion, abdominal pain, and flatulence at follow-up

with a shift in the dominant strains of microbiome, reduction in beneficial bacteria, increase of facultative anaerobic bacteria, and a decrease in the availability of total short chain fatty acids.[15] Age-related changes in the gut microbiota are associated with the physiological changes in the GIT, as well as in dietary patterns, with a concomitant decline in the normal function of the digestion leading to symptoms of indigestion.[16] Family physicians have a primary role in treating indigestion. Indigestion can be treated initially by lifestyle changes. Lifestyle modifications include avoiding foods that trigger indigestion, eating five or six small meals a day instead of three large meals, reducing or eliminating the use of alcohol and caffeine, avoiding certain pain relievers, such as aspirin, ibuprofen, and naproxen sodium, and controlling stress and anxiety.[17] Definitive treatment includes supplementation of digestive enzymes, acid suppressive therapy with proton pump inhibitors or digestive enzymes, prokinetic agents, and 5-HT1 agonists.[18] Limitations of these drugs include incomplete cure, recurrence, relapse, and associated adverse drug reactions. Therefore, there is a need for new therapy which can overcome the limitations of the current therapy.

Probiotics are constantly growing popular in the treatment of gastrointestinal disorders due to overwhelming evidence that is available and also due to lack of detrimental adverse drug reactions with them. Studies have shown that probiotics help in the improvement of symptoms of gastrointestinal disorders like abdominal pain, flatulence, bloating, and indigestion.

In our study, we evaluated the efficacy and tolerability of probiotic *Bacillus coagulans* GBI 30, 6086 with digestive enzymes in improving indigestion, reducing abdominal pain and flatulence in geriatric population. Baseline and demographic characteristics were similar in both groups. The mean age of the patients in control group is 61.08 ± 5.83 which is comparable with the study group, i.e. 64.2 ± 5.8 and the difference is statistically insignificant (p = 0.0656). The modified version of the Glasgow dyspepsia severity score (MGDSS) at baseline in the control group is 8.84 ± 1.49 and the study group is 9.08 ± 1.706. Baseline mean MGDSS in both groups are comparable without statistically significant difference between them. In control group, the follow up mean MGDSS is 7.96 ± 1.54 whereas in study group it is 4.16 ± 1.9. When the comparison is done for follow-up MGDSS between control group and study group, the results are statistically significant with $P < 0.001$ showing that probiotics have reduced the indigestion significantly. The change in the score from baseline to follow up is also statistically significant with $P < 0.0001$ in the study group. This is similar to the results of the study done by Shafaghi A *et al.*, where probiotics reduced the MGDSS from baseline to follow up.[19]

Improvement in indigestion is seen in 28% of the subjects in the control group and 60% in the study group. Upon comparison, improvement in indigestion is statistically significant in the study group with $P = 0.045$. In a study by Devendra A. Khandke, there was an improvement in indigestion in 87% of the patients who received digestive enzymes. In study done by Kleveland PM *et al.*, digestive enzymes alone were given for a period of 24 days and there was no improvement in the symptoms of indigestion or dyspepsia.[20] In our study, *Bacillus coagulans* was given along with digestive enzymes significantly reduced indigestion.

Improvement in abdominal pain was seen in 20% of the subjects of the control group and 56% of the study group which is statistically significant with $P = 0.0186$. Our results are similar to the results in a study done by Douglas S Kalman *et al.*, in which *Bacillus coagulans* was effective in abating the abdominal pain and also in another study done by Mehran Rogha *et al.*, in which *Bacillus coagulans* had decreased abdominal pain frequency which is statistically significant with $P = 0.016$.[21,22] Improvement in flatulence was seen in 20% of the subjects in the control group whereas 68% of the subjects in the study group were relieved from flatulence. Our results are similar to the results of the study done by Douglas S Kalman *et al.*, where *Bacillus coagulans* improved the Gastrointestinal Symptom Rating Scale (GSRS) subscores for intestinal gas over four weeks of use of *Bacillus coagulans*.[21] The tolerability of symbiotic was assessed by adverse event monitoring and also by other hematological and biochemical parameters like random blood sugar, urea, and creatinine. All these parameters did not show significant changes in both the groups during the study period. Eight patients of the control group and six patients of the study group experienced the adverse effects like headache, nausea, vomiting, and myalgia. The study drug did not produce any major side effects. Causality assessment done using WHO-UMC causality assessment scale showed that these adverse drug reactions are possible with the study drug.

Conclusion

In this open-label, randomized, prospective study, *Bacillus coagulans* along with digestive enzymes has shown to improve the indigestion, abdominal pain, and flatulence which is evaluated using the Modified version of the Glasgow dyspepsia severity score and also subjectively. It is well tolerated and safe to be used in geriatric patients without any major adverse effects. This combination of *Bacillus coagulans* and digestive enzymes like amylase, pepsin, and lipase is thus proven to be effective in treating indigestion in geriatric patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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