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ORIGINAL ARTICLE

Does oral α-galactosidase relieve irritable bowel symptoms?

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Abstract

Objective. Abdominal bloating is reported by a majority of irritable bowel syndrome (IBS) patients. Excess colonic fermentation may cause gaseous symptoms. Several foodstuffs contain oligosaccharides with an α-galactosidic linkage that is resistant to mammalian hydrolases. Assisted hydrolysis by exogenous α-galactosidase enzyme (AG) could offer a way of controlling IBS symptoms by reducing colonic fermentation and gas production. The aim of this study was to assess the effect of AG on symptom severity and quality of life in IBS patients with abdominal bloating or flatulence. ***Methods.*** A total of 125 subjects with IBS received AG or placebo at meals for 12 weeks. IBS-Symptom Severity Score (IBS-SSS) and quality of life (QoL) were assessed at baseline, during the treatment and at 4-week follow-up. ***Results.*** AG showed a trend toward a more prominent decrease in IBS-SSS. The responder rate at week 16 was higher for the AG group. No difference was detected in QoL between AG and placebo groups. A total of 25 patients (18 in AG group and 7 in placebo group, $p = 0.016$) withdrew from the study. Abdominal pain and diarrhea were more often reported as reason for withdrawal in AG group. ***Conclusions.*** We found no evidence to support the use of AG routinely in IBS patients. Improvement of clinical response at 4-week follow-up may suggest a long-term effect of unknown mechanism, but could also be attributed to non-responder drop out. Gastrointestinal (GI) side effects may be a coincidence in this study, but irritation of GI tract by AG administration cannot be excluded.

Key Words: *abdominal pain, α-galactosidase, carbohydrates, diet, flatulence, irritable bowel syndrome*

Introduction

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal (GI) disorder with abdominal pain or discomfort and abnormal bowel habits in the absence of organic abnormalities [1–3]. It lowers the quality of life (QoL) as much as many organic diseases and increases burden on health-care services [4,5].

More than 60% of IBS patients report symptom exacerbation after food ingestion. Dietary symptom triggers include cabbage, onion, peas, beans, hot spices and coffee [6]. Reducing the amount of non-absorbable FODMAPS's (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) in the diet alleviates IBS symptoms, especially those related to excess gas formation due to colonic fermentation of carbohydrates [7].

One of the most bothersome symptoms in IBS is abdominal bloating, which is reported by >80% of patients [8]. Abdominal bloating in IBS may result from excess colonic fermentation with consequent gas production [9,10] or abnormal intestinal gas transit [11] and impaired tolerance of normal gas loads due to visceral hypersensitivity [12].

Gas production in the bowel is a normal physiological phenomenon as unabsorbed carbohydrates are fermented by colonic bacteria, which leads to the generation of gases such as carbon dioxide, methane and hydrogen.

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Many cereals, pulses, legumes, fruits, nuts and vegetables contain raffinose, stachyose and verbascose. These oligosaccharides have an α-galactosidic linkage, which is resistant to mammalian hydrolases. Assisted hydrolysis of indigestible oligosaccharides by exogenous α-galactosidase (AG) enzyme could offer a potential means of controlling IBS symptoms by reducing colonic fermentation and gas production. AG is a natural enzyme of fungal origin, derived from *Aspergillus niger*.

In a previous randomized double-blind cross-over trial, AG reduced flatulence after a carbohydrate-rich meal in healthy volunteers [13]. Moreover, AG reduced flatulence and hydrogen excretion in the breath among type 2 diabetics with iatrogenic carbohydrate malabsorption that was induced by oral acarbose administration [14]. In a double-blind, placebo-controlled trial, 1200 GaIU of AG reduced both breath hydrogen excretion and the severity of flatulence among healthy volunteers after a challenge meal that contained a high amount of fermentable substrate from cooked beans [15].

No published data are available on the effect of AG on gaseous symptoms in IBS as far as we are aware. The aim of our study was to assess the effect of AG on symptom severity and QoL in IBS patients who suffer from abdominal bloating or flatulence as their most disturbing symptoms.

Methods

Study design

The study was a randomized, double-blind and placebo-controlled design. Subjects were randomized to receive AG treatment or placebo for 12 weeks, followed by a 4-week follow-up period. The study protocol was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa. The trial was registered at the US National Institutes of Health (Clinical Trials.gov) #NCT01243853.

Study population

The eligibility criteria included subjects aged 18–65 years who had IBS as defined by the Rome III criteria [16], and had abdominal bloating and/or flatulence as their most disturbing symptoms. An ileocolonoscopy with normal macro- and microscopic findings was required in their medical history within the previous 5 years. Exclusion criteria included an organic GI disease, such as inflammatory bowel disease, major abdominal surgery, any malignancy, pregnancy or breastfeeding, and any changes in the regular medication during the 4 weeks prior to the commencement of the study. Inclusion criteria allowed subjects who had celiac disease and who had been consuming a gluten-free diet for at least 1 year, and also subjects with lactose malabsorption on a lactose-free diet.

Subjects were recruited from a private outpatient clinic (Gastrolääkärit OY), and public health gastroenterology outpatient clinics in Hospital District of Helsinki and Uusimaa, and also by means of a newspaper advertisement. Study candidates were pre-screened by a study nurse. Those meeting the preliminary inclusion criteria by telephone interview were subsequently referred to a physician's screening visit to assess further their eligibility for the study. Blood count, sedimentation rate, transglutaminase antibodies for celiac disease, and thyroid function tests were performed at the physician's screening visit, if these tests had not already been performed within 1 year. The subjects were weighed before and after the treatment period to indicate if any hydrolysis of oligosaccharides into more digestible carbohydrates by AG could lead to weight gain. They were provided with the obligatory written, informed consent forms on which they all gave their signatures.

The subjects completed a Finnish translation of the previously validated IBS-Symptom Severity Score (SSS) [17] at baseline before the treatment period, after 4, 8 and 12 weeks of treatment, and finally after the 4-week follow-up period. A score of <75 indicates no symptoms, 75–175 indicates mild disease, 175–300 moderate disease and >300 stands for severe disease. A reduction of 50 points indicates clinically significant improvement [17]. In IBS-SSS, besides of items assessing abdominal pain, only one item (severity of abdominal distension) assesses gaseous symptoms. To acquire more data on gaseous symptoms, an extra visual analog scale item assessing severity of flatulence was added into the IBS-SSS questionnaire. Because the item was not formally validated, it was not included in the IBS-SSS; instead it was defined as a secondary outcome variable. Each study subject also filled in a Finnish language version of the IBS-QoL [18] at baseline, after 12 weeks of treatment, and at the 4-week follow-up.

The primary outcome variable was the change of IBS-SSS from the baseline during the treatment and follow-up periods. The change from baseline in IBS-QoL overall score, the percentage of responders, the severity of flatulence and individual components of the IBS-SSS were the secondary outcome variables. A responder was defined as a subject with at least 50 points decrease in IBS-SSS during the study period.

Table I. Demographic and symptom characteristics of AG and placebo groups.

	AG (n = 63)		Placebo (n = 62)		p-Value
Female, n (%)	43	(68.3)	43	(69.4)	NS
Mean age, years (SD)	49.8	(13.0)	49.1	(13.3)	NS
Mean weight at baseline, kg (SD)	75.5	(17.6)	77.0	(15.1)	NS
Smoker, n (%)	7	(11.1)	6	(9.8)	NS
Weekly alcohol intake, units (SD)	3.2	(4.5)	3.0	(4.5)	NS
IBS symptom severity at baseline, SSS score (SD)	246.2	(77.5)	245.1	(72.7)	NS
No IBS medication, n (%)	32	(50.8)	33	(53.2)	NS
Mild symptoms, n (%)	1	(1.6)	0	(0)	NS
Moderate symptoms, n (%)	43	(68.3)	49	(79.0)	NS
Severe symptoms, n (%)	19	(30.2)	13	(21.0)	NS

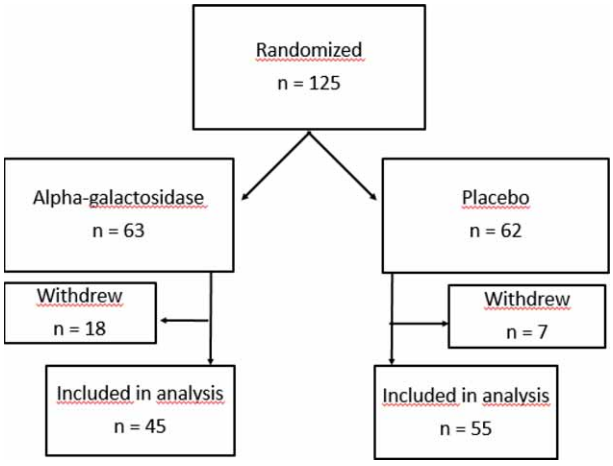

Figure 1. Flow chart of the study.

Sample size

The sample size was calculated based on an assumption of a 30% placebo effect and a clinically significant 25% treatment effect over placebo. A two group χ^2 test with a 0.05 two-sided significance level with 80% power was used to detect this difference and this yielded a sample size of 62 for each group.

Randomization and intervention

The study subjects were randomly assigned into four blocks to receive either three capsules of AG containing 400 GaIU/capsule (Nogasin®/Verman OY, Finland) or placebo in identical looking capsules three times a day: with breakfast, lunch and dinner. The patients, physicians and study nurse were blinded regarding the study group by using randomly generated codes that were kept confidential until data collection was completed.

Statistical analysis

The primary and secondary outcome variables were analyzed by repeated measures analysis of variance (RM ANOVA). Incomplete observations were assumed to be missing data in the model. Chi-square statistics were used to compare the frequencies of various demographic characteristics and rates of responders between AG and placebo groups. The Two-sample T-test was used to compare the weight of the subjects at the beginning and in the end of the study. A two-sided p-value <0.05 was considered statistically significant.

Results

A total of 127 subjects met the preliminary inclusion criteria. After the screening visit, 125 subjects (86 females, 39 males) participated in the study. No differences were detected in demographic and symptom severity parameters between subjects in active (n = 63) and placebo (n = 62) groups (Table I). However, QoL at baseline was somewhat higher in the AG group, 70.2 versus 61.0, p = 0.005.

Of the 125 subjects, 25 withdrew from the study; 18 (28.6%) in the AG group, and 7 (11.3%) from the placebo group (p = 0.016) (Figure 1). The treatment period was completed by 101 subjects; one subject withdrew before the follow-up visit. Demographic factors, such as gender, age, education, tobacco or alcohol use, duration of IBS symptoms, concomitant chronic illness, or the use of pain killers, were not different among those who withdrew compared to those who continued the study. In the AG group, abdominal pain (n = 4 vs. 0 in placebo) and diarrhea (n = 2 vs. 0 in placebo) were more often reported as the reason for withdrawal. Abdominal bloating or flatulence was reported as the reason for withdrawal from the placebo group by two subjects, but none in AG group.

Both the AG and the placebo groups showed a substantial decrease in SSS during the intervention. The mean decrease in IBS-SSS was 67.0 in the AG group and 47.2 in the placebo group at 12 weeks. No significant difference was, however, detected for the symptom profiles between the groups using the

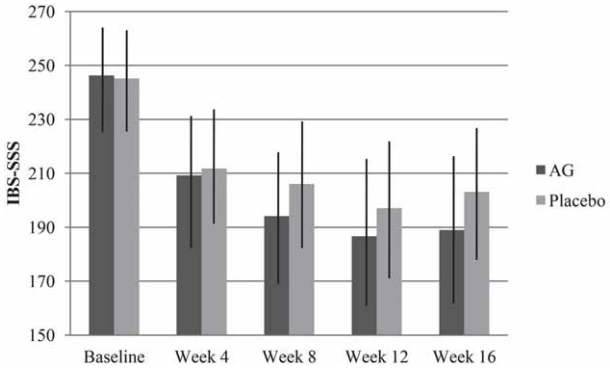

Figure 2. IBS-symptom severity score during treatment and follow-up, p = 0.63 AG versus placebo (RM ANOVA). Bars represent 95% confidence intervals.

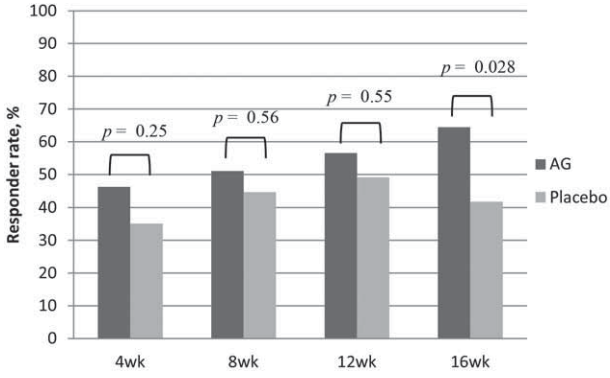

Figure 3. Responder rates in AG and placebo groups during treatment and follow-up.

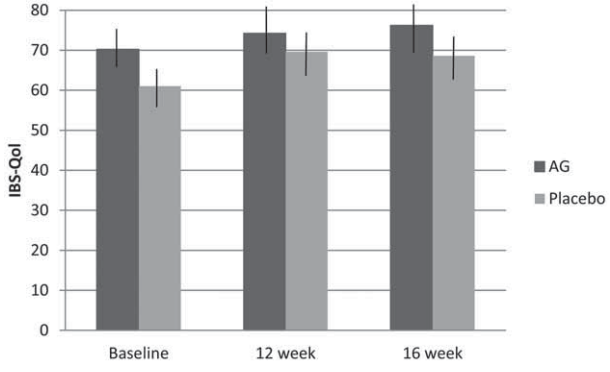

Figure 4. Quality of life in AG and placebo groups, p = 0.42 AG versus placebo (RM ANOVA). Bars represent 95% confidence intervals.

ANOVA model, although the AG group showed a trend toward a more prominent decrease in IBS-SSS during the whole treatment period and follow-up (Figure 2). No gender differences were detected in the IBS-SSS scores between AG and placebo at any point.

None of the individual components in the IBS-SSS improved for the AG group compared to the placebo group. The decrease in abdominal distension score from the baseline to 12 weeks was 12.2 points (95% CI 4.6 – 19.8) for the AG group, and 4.6 (95% CI 3.0 – 12.3) for the placebo group. The flatulence score at 12 weeks had decreased by 11.0 points (95% CI 4.3 – 17.7) for the AG group and 15.3 points (95% CI 7.4 – 23.2) for the placebo group.

The percentage of responders was higher for the AG group after the 4-week follow-up period, but not during the treatment period (Figure 3).

During the treatment period, no difference was detected in QoL profiles between AG and placebo groups (Figure 4).

A slight gain in mean weight occurred for both groups during the study period: 0.33 kg for the AG group, and 0.67 kg in the placebo group (p = 0.62).

Discussion

This is the first clinical trial to our knowledge that studied the effect of AG on IBS symptoms. No statistically significant difference was detected in the symptom profiles and QoL compared to placebo in the present study. However, a trend toward a more prominent decrease in IBS-SSS scores was detected for the AG group. In addition, the AG group showed a higher rate of responders than the placebo group at the end of the study.

Associations between carbohydrate malabsorption, gas formation and gaseous symptoms have been shown in earlier studies [14,15]. Gaseous symptoms in IBS may also arise from insufficient clearing of gases, or visceral hypersensitivity inducing symptoms even with normal levels of GI gas [11,12]. All these mechanisms are possible targets for medical treatment. Modification of intestinal bacterial flora by probiotics or by antibiotics such as rifaximin may reduce colonic fermentation and gas production [19,20]. AG has been shown to decrease both gas formation and GI symptoms in healthy volunteers [15].

Our study found a tendency toward a more prominent decrease of IBS symptoms for the AG group, which had a SSS of 15–20 points lower than placebo group at every time point during the treatment period and follow-up. The SSS had decreased by 67 points for the AG group compared with 47 points for the placebo group at the end of the treatment period. A decrease of >50 points has been regarded as clinically significant [17]. The sample sizes of AG and placebo groups used in this study were insufficient to detect statistically significant results in the main outcome measure over placebo. This may partly be due to a high responder rate of up to

49% for the placebo group, and also due to the higher than expected rate of drop-outs from the AG group, which reduced the statistical power of the study. Despite the fact that all our patients had abdominal bloating or flatulence as the most disturbing symptoms, GI gas formation *per se* was not measured. Therefore, it is possible that some patients had other mechanisms than excess gas such as visceral hypersensitivity or abnormal gas handling that caused their bloating symptoms. In addition, IBS patients have shown abdominophrenic dyscoordination involving activity of the abdominothoracic wall, resulting in abdominal distension [21]. They would be less likely to benefit solely from decreasing gas formation. Overall, the proportion of IBS patients having excess gas formation as the main mechanism for abdominal bloating is not known. It is possible that this subgroup of IBS patients could benefit from AG, but this needs further study.

Along with oligosaccharides hydrolyzed by AG, a western diet also includes other non-digestible fermentable carbohydrates such as fructose, fructans and polyols. Therefore, it is possible that the gas reducing effect of AG in our study was partially counteracted by the presence of other gas producing carbohydrates, explaining the modest result for AG.

The response rate for the AG group was significantly higher than for the placebo group at the end of the study, that is, after the 4-week follow-up period had elapsed, but not during the intervention period itself. This may suggest a long-term effect with an unknown mechanism: the modification of bacterial flora is one possible mechanism, but it may also be due to a higher proportion of non-responder drop-outs in the AG group.

A significantly higher proportion of subjects of the AG group withdrew from the study. They reported more abdominal pain and diarrhea as the reason for withdrawal. This might be only a co-incidence in our study since the numbers were low. However, irritation of the GI tract by the relatively high dose of AG, 1200 GaIU t.i.d, cannot be ruled out.

In conclusion, we did not find clinically significant evidence to support the use of AG routinely in IBS patients, although some patients with excess gas formation due to dietary fermentable substrates might benefit from it.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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