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A randomized double-blind placebo-controlled clinical trial on efficacy and safety of association of simethicone and *Bacillus coagulans* (Colinox®) in patients with irritable bowel syndrome

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Abstract. – INTRODUCTION: Irritable bowel syndrome (IBS) is a chronic gastrointestinal (GI) disorder that affects 15-20% of the Western population.

BACKGROUND: There are currently few therapeutic options available for the treatment of IBS. The aim of this study is to evaluate the efficacy and the safety of a medical device containing a combination of Simethicone and *Bacillus coagulans* in the treatment of IBS.

PATIENTS AND METHODS: This is a monocentric double-blind, placebo-controlled parallel group clinical trial. Adult subjects suffering from IBS as defined by Rome III criteria were enrolled. Bloating, discomfort, abdominal pain were assessed as primary end point. Subjects received the active treatment or placebo 3 time a day after each meal for 4 weeks of study period. Subjects were submitted to visit at Day 0 (T1), at Days 14 (T2) and 29 (T3).

RESULTS: Fifthy-two patients were included into the study. Intragroup analysis showed a significant reduction of the bloating, discomfort and pain in Colinox® group (CG) compared to placebo group (PG). Between group analysis confirmed, at T1-T3, significant differences between CG and PG in bloating and discomfort.

DISCUSSION: Simethicone is an inert antifoaming able to reduce bloating, abdominal discomfort. Literature offers increasing evidence linking alterations in the gastrointestinal microbiota and IBS and it is well known that probiotics are important to restore the native gut microbiota. The Colinox medical device is specifically targeted against most intrusive symptom of IBS (bloating) and it is also able to counteract the most accredited ethiopathogenetic factor in IBS (alterations of intestinal microbiota).

CONCLUSIONS: This is the first randomized double-blind placebo-controlled clinical trial demonstrating the efficacy and safety of a combination of simethicone and *Bacillus coagulans* in treatment of IBS.

Key Words:
Irritable bowel syndrome, Simethicone, Probiotics, *Bacillus coagulans*, Medical device.

Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by recurrent abdominal pain or discomfort and change in bowel habits[1], in the absence of identifiable organic cause[2]. Bloating, distension, and disordered defecation are commonly associated features[3]. IBS affects 15-20% of the Western population, with a higher prevalence among women[1,4]. It is the most common diagnosis made by gastroenterologists[5]. Hungin et al[6] underlined as European prevalence for IBS adjusted for variations in population size between countries, was 4.8%, ranging individually from 11.5% in Italy to 1.7% in Germany. Common IBS symptoms for which no endoscopic, biochemical or radiological cause is verifiable are abdominal pain, flatulence and bloating. In particular, abdominal bloating is the commonest symptom (up to 96% of patients) of irritable bowel syndrome (IBS)[7]. Agrawal et al[8] emphasize how abdominal bloating is an extremely intrusive symptom, which characteristically varies in severity, increases during the course of the day, tends to get worse after meals, and usually subsides overnight[7-9]. IBS is not life threatening; however, the symptoms can severely impact the emotional health, functional ability and quality of life of patients. According to a large Internet-based survey, IBS has a consistently negative impact on quality of life[4]. Like-

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wise, social activities such as eating out, taking long trips and holidays were hindered by symptoms of IBS[5]. Unfortunately, there are currently few therapeutic options available for the treatment of IBS[10]. Current therapeutic strategies (spasmolytics or antidepressants at low doses for the pain, anti-diarrhea agents or 5HT3 antagonists for diarrhea, lubiprostone, linaclotide, bulk-forming laxatives or 5HT4 agonists for constipation) are often unsatisfactory[2]. In addition some of these drugs could show side effects that suggest a careful use of them[11]. This lack of treatment options, together with the high prevalence of IBS and its associated debilitating disease burden, have sparked considerable interest in the use of probiotics, live bacteria that are beneficial to the host, to help relieve symptoms of IBS. Patients with IBS, diagnosed through the Rome III criteria, are classified as possessing diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C) or alternating symptoms (sometimes diarrhea, sometimes constipation) and undefined IBS[2]. Symptoms can occur in response to infection, changes in diet, lifestyle changes or psychological stress[12]. A significant number of IBS patients report postprandial symptoms; however, the interaction of food and intraluminal content with secretory, motor and sensory mechanisms is poorly understood[13].

While the exact pathophysiology of IBS is unknown, it is believed to result from a dysregulated and excessive immune response to components in the GI microflora, which leads to a sustained inflammatory response and mucosal damage[14]. Both retrospective and prospective studies have documented the onset of IBS following bacterial gastroenteritis, which is more common among patients with IBS-D[15]. Other studies have provided evidence of low-level mucosal inflammation and immune activation in patients with IBS[16,17]. In addition, it has been shown that the fecal flora of IBS patients differs from that of normal patients. Patients with IBS may harbor bacterial overgrowth and their symptoms may be ameliorated by its eradication[18]. Probiotics have been demonstrated to normalize or rebalance the GI microflora status quo, restoring gut epithelial function and the mucosal immunological barrier[19]. Simethicone is an inert substance with antifoaming activity that reduces bloating, abdominal discomfort, and abdominal pain by promoting the clearance of excessive gas along the gastrointestinal tract[20]. Aim of our preliminary study was to evaluate the efficacy and the safety of an association of Simethicone and *Bacillus coagulans* (Colinox®) in form of tablets in the treatment of IBS symptoms compared to placebo.

Patients and Methods

Study Design

A monocentric double-blind, placebo-controlled parallel group clinical trial was conducted from October 2012 to April 2013 in the Department of Internal Medicine and Gastroenterology, Complesso Integrato Columbus, Catholic University of the Sacred Heart (Rome, Italy). This study, which adhered to the tenets of the Declaration of Helsinki, was conducted in accordance with the current International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines and was approved by the local Ethics Committee. Documentation notifying clinical investigations using medical devices bearing CE marking was registred to Italian Ministry of Health.

Voluntary outpatients patients were enrolled. Before entry, patients received detailed information on the study by investigators and signed a written consent form. All investigators and subjects was blinded throughout the trial.

Population

Subjects were eligible for inclusion if they met the following criteria: adult patient (aged 18-75 years), suffering from IBS as defined by Rome III criteria (recurrent abdominal pain or discomfort with onset at least 6 month prior to diagnosis, associated with 2 or more of the following, at least 3 d/months in the last 3 mo: improvement with defecation; onset associated with change in frequency of stool; onset associated with change in form (appearance) of stool[1]. Exclusion criteria were: pregnant or breastfeeding women, active heart disease, uncontrolled high blood pressure, renal or hepatic impairment, type 1 or 2 diabetes mellitus, psychiatric and immune disorders, unstable thyroid disease, Parkinson's disease, history of cancer, previous stomach or intestinal surgery, cardiological disease, allergy to simethicone, *Bacillus coagulans* or other ingredients present in medical devices or placebo. The eligible subjects that during the screening consumed medication or supplements interfering with the natural flora of the gut such as antibiotics, probiotics, or prebiotics will be included in the study

only after 15 days wash out period. Patients satisfying the eligibility criteria were randomized to assume medical devices or placebo, in a 1:1 ratio. Treatment was characterized by numerical code. Simple randomization sequence was obtained by random number generator software. Randomization list was elaborated by a third party not involved in the enrollment and assignment of the treatment. Only after the signing of the informed consent and clinical assessment as per phase T1 the subjects were associated to the treatment according to the randomization list (secured in a deposit box). Predetermined withdrawal criteria were: assumption during the trial of antibiotics, probiotics or drugs or supplement which interfere with study results, intercurrent pregnancy. The primary efficacy endpoint was the magnitude of change of abdominal pain, discomfort, bloating. The secondary efficacy endpoint were the stool assessment and patients' global judgement of treatment. The mean number of bowel movements per day were also analysed.

Treatment

Patients were randomized to receive either the treatment or placebo three time a day after each meal for 4 weeks of study period. Subjects were submitted to three control visits over the course of four weeks – a screening/randomization visit at Day 0, and two follow-up visits at Days 14 and 29. Both investigators and subjects were blinded to product assignment. During the study period all the involved subjects assumed at their home a tablet of the assigned product (medical device or placebo) after the three daily meals.

Timing

The study developed into 3 consecutive evaluation phases: T1, T2 and T3.

T1

Enrolled subjects underwent a clinical baseline assessment physical examination, Visual analogic Scales and Bristol stool scale and mean number of bowel movements per day. After clinical baseline assessment the subject was assigned to treatment.

T2 (day 14)

At the end of the first 2 weeks of therapy, patients in each group underwent the same assessment as T1 and it was performed a registration of any side effects.

T3 (day 29)

At the end of the first 2 weeks of therapy, patients in each group underwent same assessment as T1 and T2 and it was performed a registration of any side effects. Patients were requested an overall assessment of received treatment.

Assessment Test

To assess the primary and secondary end point were used validated self-administration scales. To assess the primary end point were used abdominal pain, discomfort, bloating Visual analogue scale (VAS) scores 0-100 mm (0 = none symptom; 100 = more severe symptom). In IBS patients, the 0-100 mm VAS of abdominal pain was shown to be a valid and a reliable tool[21,22]. To assess change in type of stools was used the Bristol Stool Form Scale[23,24]. We asked to each patient the mean number of bowel movements per day (absolute frequence). A 4-point Likert scale (very good, good, fair, no effects) was used to evaluate subjects treatment overall assessment. Adverse effects were also recorded at T2 and T3 phases.

Medical Device Description

Colinox® (DMG Italia S.r.l.) belongs to class IIa medical devices applying the rule 5 of annex IX is a medical device according to the Directive 93/42/EEC on medical devices and subsequent amendments.

Colinox® is a medical device with mechanical and physical action indicated in the treatment of irritable bowel syndrome. The main component are simethicone and spores of *Bacillus coagulans*. Simeticone is a mixture of liquid dimeticones containing silicon dioxide to enhance the defoaming properties[25]. The rational of use of simethicone in IBS is given by the gas retention and excessive gas production demonstrated in this syndrome[8,22,26,27]. Some studies suggest the probiotic *Bacillus coagulans* decreases that symptoms of abdominal pain and bloating in subjects with IBS particularly abdominal pain and distention in the post-prandial period[28,29].

Placebo Description

Placebo is pharmacologically inert but clinically active in this syndrome[30]. Therefore, it was decided to choose this design for the study, respecting what is highly recommended by Akehurst and Kaltenthaler[31] (all the studies on the IBS should be randomized, double blind, placebo-controlled). In addition in placebo group are

not expected particular side effects (except for an allergic reaction to the excipient of the product). The placebo was provided by the manufacturer and matched in size and color to the active product (medical device). The placebo formulation included only the excipient present in active treatment. Packaging of placebo was identical to that active treatment.

Sample Size Calculation

For the sample size calculation it was followed a conservative criteria assuming that the variability of the results is approximately more than 50% compared to the values of the clinical trial of Wittmann et al[22]. We planned a study of a continuous response variable from independent control and experimental subjects with 1 control(s) per experimental subject. In a previous study of Wittmann et al[22], the response within each subject group was normally distributed with standard deviation 10. If the true difference in the experimental and control means is 10, we will need to study 22 experimental subjects and 22 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05. To calculate the sample size we used PS version 3.0.12 by Dupont and Plummer[32].

According to literature drop out data of 15%[22], we enrolled 26 experimental subjects and 26 control subjects, achieving total number of 52 subjects.

Statistical Analysis

The statistical analysis was conducted using the Friedman and the Wilcoxon tests to assess the overall and the time specific intra group treatment effect, respectively. About the multiple comparisons performed by Wilcoxon tests, Bonferroni correction was considered significant only those comparisons for which $p \leq .05/3 = .0166$. Between groups analysis was performed a Mann Whitney test. Differences were considered statistically significant at $p \leq .05$. Data are reported as means ± SD, ranges or absolute frequency as appropriate. The Bristol Score Scale used to evaluate the quality of stools was considered as a nominal variable. Actually, both the opposite ends of the scale are abnormal conditions, with low values and high values indicating extremely harsh and quite watery stools, respectively. Similarly, none daily evacuation identifies constipation and two or more evacuations per day an excessive frequency of evacuation. On this basis, we built a dichotomous variable that was set to 1, when the Bristol score was between 3 and 5 and the frequency of daily evacuations was 1 or 2, and to 0 in all other cases. Moreover, one more dichotomous variable was set to 1, to identify the achievement of a normal evacuation at the last visit starting from an abnormal situation during the previous visits, or to 0, to identify stable or deteriorating evacuation quality and frequency during the study. Also the subjective treatment overall assessment was dichotomized according to the following rule: very good or good = 1, otherwise (fair, no effects) = 0. To evaluate the between treatments difference of the frequency of those dichotomous variables we used the Fisher's two sided exact test. Intention to treat analyses were performed. Analyses were performed using SAS Version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 52 subjects were included into the study and were successfully randomized to receive either placebo group (N = 26) or active treatment (Colinox® group) (N = 26) (18 M and 34 F), as expected from the sample size calculation for this study. After a randomization a subject withdrawn from the study before beginning the treatment; she had been replaced. All the subjects who began the treatments (52 subjects) ended the clinical study, demonstrating a high adherence to treatments.

Anthropometric baseline population data are summarized in Table I. Notably female/male ratio in our entire sample was 2:1 confirming the epidemiological data of literature[33].

Primary Outcome

The mean values (SD) of the scores taken from the VAS scales applied to the three variables (bloating, discomfort and pain) defined as the primary outcome of the study, stratified by time and treatment are shown in Table II.

Intragroup Analysis

The analysis highlighted a statistically significant and clinically relevant reduction of the bloating in CG (T1 = 77.7 ± 26.1; T3 = 38.6 ± 29.3; $p = .0001$) whereas the reduction in PG was not clinically significant (T1 = 72.3 ± 30.1; T3= 71.3 ± 28.0; $p = .037$).

Table I. Baseline characteristics of entire sample, Colinox group, placebo group.

Characteristics	Entire sample	CG	PG
N° of subjects	52	26	26
N° of subjects submitted to wash out period	5	1	4
Median age (years ± SD)	39 ± 14.3 (20-73)	42 ± 15.9 (20-73)	36 ± 12.1 (20-64)
Sex	18 M/ 34/F	4 M/22 F	14 M/12 F
Height (cm)	169 ± 9.6 (140-191)	166 ± 7.2 (151-182)	173 ± 10.5 (140-191)
Weight (kg)	64 ± 11 (38-88)	61 ± 10.6 (38-80)	68 ± 11.6 (45-88)

Note: Value are expressed as mean ± standard deviation or ranges or absolute frequency as appropriate. *Legend:* CG = Colinox® group; PG = Placebo group; SD = standard deviation; M= male; F = female; cm = centimeter; kg = kilogram.

Similarly, discomfort in CG reduced in statistical and clinical significant manner (T1 = 62.0 ± 22.7; T3 = 33.7 ± 23.3; p = .0001) whereas in PG the reduction was not statistically nor clinically significant (T1 = 70 ± 20.8; T3 = 68.6 ± 20.2; p = ns).

At last in CG pain VAS significantly reduced (T1 = 37.8 ± 31.4; T3 = 22.8 ± 25.2; p = .002); not significant reduction was recorded in PG (T1 = 31 ± 21.0; T3 = 30.9 ± 23.1; p = ns).

Between Group Analysis

Figure 1 shows the timing of VAS bloating score modification in CG and PG. Specifically, not statistical significant differences were recorded at T1 between two groups, with baseline mean score slightly worse in CG (CG = 77.7 ± 26.1 vs PG = 72.3 ± 30.1; p = ns). At T2 we noted a significant better VAS score in CG compared to PG (CG = 52.2 ± 28.6 vs PG = 69.2 ± 30.3; $p < .05$). At T3 the difference between CG and PG was further increased (CG = 38.6 ± 29.3 vs PG = 71.3 ± 28.0; $p < .01$).

Figure 2 shows the timing of VAS discomfort score modification in CG and PG. Briefly, we did not recorded any significant differences between two groups at T1 (CG = 62 ± 22.7 vs PG = 70 ± 20.8; p = ns). On the contrary, at T2 (CG = 46 ± 25.4 vs PG = 68.1 ± 21.1; $p < .05$) and T3 (CG = 33.7 ± 23.3 vs PG = 68.6 ± 20.2; $p < .01$) CG showed a significantly better VAS score compared to PG.

Figure 3 shows the timing of pain VAS score modification in CG and PG. None statistically significant differences were recorded between two groups at T1 (CG = 37.8 ± 31.4 vs PG = 31 ± 21; p = ns), T2 (CG = 23.8 ± 26.6 vs PG = 31.3 ± 23.1; p = ns), T3 (CG = 22.8 ± 25.2 vs PG = 30.9 ± 23.1; p = ns).

Secondary Endpoint

The secondary end point analysis was performed in 26 CG subjects and in 25 PG ones (Bristol scale data from one subject in PG were missing in all study phases).

Table II. Primary outcomes in Colinox group and placebo group: VAS scores as mean value (SD).

Timing	T1	T2	T3	F	W1-2	W1-3	W2-3
Bloating							
CG	77.7 (26.1)	52.2 (28.6)	38.6 (29.3)	.0001	.0001	.0001	.0001
PG	72.3 (30.1)	69.2 (30.3)	71.3 (28.0)	.037	ns	ns	ns
Discomfort							
CG	62.0 (22.7)	46.0 (25.4)	33.7 (23.3)	.0001	.0001	.0001	.001
PG	70.0 (20.8)	68.1 (21.1)	68.6 (20.2)	ns	ns	ns	ns
Pain							
CG	37.8 (31.4)	23.8 (26.6)	22.8 (25.2)	.002	.003	.001	ns
PG	31.0 (21.0)	31.3 (23.1)	30.9 (23.1)	ns	ns	ns	ns

Note: Values are expressed as mean ± standard deviation. Significant p value ≤ .05. In multiple comparisons performed by post hoc Wilcoxon test it was used Bonferroni correction (p was setted ≤ .05/3 = .0166). *Legend:* F = Friedmann test; W1-2 = post hoc Wilcoxon test (T1 vs T2); W1-3 = post hoc Wilcoxon test (T1 vs T3); W2-3 = post hoc Wilcoxon test (T2 vs T3); CG = Colinox® group; PG = Placebo group; ns = not significant.

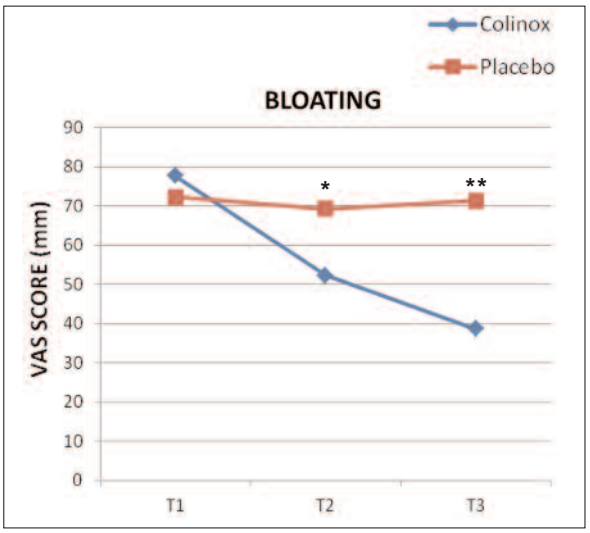

Figure 1. Bloating: VAS score in CG and PG. *Note:* Between groups analysis. *Legend:* mm = millimeter; *$p \leq .05$; **$p \leq .01$.

Data analysis showed a significant improvement of the evacuation quality in CG compared to PG ($p < .001$) (Pearson chi^2(3) = 34.3333; Pr = .000 Fisher's exact = .000).

Treatment Overall Assessment

A 69.2% of CG subjects referred a positive treatment overall assessment (very good = 26.9% + good = 42.3%) compared to 3.8% of PG (very good = 0 + good = 3.8%) subjects ($p < .001$) (Pearson chi^2(1) = 23.9681; Pr = .000 Fisher's exact = .000) (Table III).

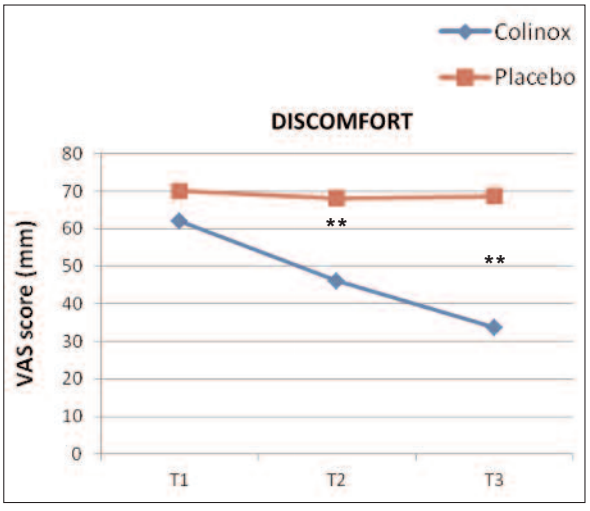

Figure 2. Discomfort: VAS score in CG and PG. *Note:* Between groups analysis. Legend: mm = millimeter; *$p \leq .05$; **$p \leq .01$.

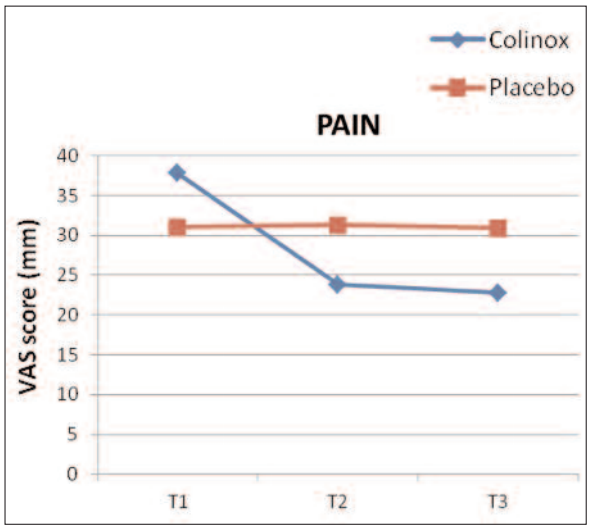

Figure 3. Pain: VAS score in CG and PG. *Note:* Between groups analysis. *Legend:* mm = millimeter; *$p \leq .05$; **$p \leq .01$.

Safety

No serious adverse effects were recorded in both groups

Discussion

Briefly, our data proved that the association of simethicone and *Bacillus coagulans* positively impacts on major symptoms (more evidently on bloating and discomfort) and on evacuation quality in IBS. More specifically we recorded a clinical and statistical significant difference in post treatment bloating and discomfort between CG and PG. Post treatment difference in pain VAS score resulted clinically and statistically significant at intragroup analysis but not at intergroups analysis, reasonably due to small sample size. Notably the placebo response of IBS patients ranged from 16.0 to 71.4% in literature, being a fulfillment of the Rome criteria for study entry

Table III. Subjective treatment overall assessment.

	CG	PG
No effects	3 (11.5%)	24 (92.3%)
Fair	5 (19.2%)	1 (3.8%)
Good	11 (42.3%)	1 (3.8%)
Very good	7 (26.9%)	0 (0%)
Total	26 (100.0%)	26 (100%)

Note: Data are expressed as number of subjects (percentage). *Legend*: CG = Colinox® group; PG = Placebo group.

significant associated with lower placebo response rates[30]. In our sample we performed a strict study entry screening using Rome III criteria which implied a not clinically significant improvement in PG, as reported in Patel meta-analysis[30]. Colinox is registered as medical device (simethicone and *Bacillus coagulans*) and, according to medical device definition[34], it does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means. It is specifically targeted against most intrusive symptom of IBS (bloating) and it is also able to counteract the most accredited ethiopathogenetic factor in IBS. Specifically simethicone is an oral antifoaming agent, with a long course use in clinical and diagnostic practice[35-39]. Simethicone is able to reduce bloating, abdominal discomfort, and abdominal pain by promoting the clearance of excessive gas along the gastrointestinal tract[40,41], alone or in association with other substances (e.g. alverine citrate, loperamide)[22,27,42,43].

Literature offers increasing evidence linking alterations in the gastrointestinal microbiota and IBS[2]; it is well known that probiotics are important to restore the native gut microbiota[44]. Major problem is the extreme susceptibility of most probiotic to acidity of the stomach, and bile acids[45]; some strains of *Bacillus coagulans*, being a spore-forming bacterium, can survive extreme conditions of gastric and duodenal environment[45-50]. A randomized, double-blind, placebo controlled clinical trial evaluated the effects of *Bacillus coagulans* GBI-30, 6086 on abdominal pain and bloating[28]. The study included 44 patients with IBS-D who received either placebo or *Bacillus coagulans* GBI-30, 6086 once a day for 8 weeks. Self-assessment of the severity of IBS symptoms was recorded daily. Results displayed statistically significant changes in abdominal pain and bloating scores from baseline for patients treated with *Bacillus coagulans* GBI-30, 6086 when compared after 7 weeks ($p < .01$). No adverse events were reported during the 8-week study period, and the investigator concluded that *Bacillus coagulans* GBI-30, 6086 may be a safe and effective adjunct therapy for the relief of abdominal pain and bloating for patients with IBS. More recently, Dolin[44] in a controlled pilot study evaluate the effects of the (*Bacillus coagulans* GBI-30, 6086) probiotic on IBS symptoms, in a randomized, double-blind, placebo-controlled clinical trial including patients with diarrhea-predominant IBS (IBS-D). Patients were randomized to receive either *Bacillus coagulans* GBI-30, 6086 or placebo once a day for 8 weeks. Patients filled out a quality-of-life questionnaire, and self-assessment diaries were provided to record stool count and consistency, symptom severity, and medication consumption. The average number of bowel movements per day was significantly reduced for patients treated with *Bacillus coagulans* GBI-30, 6086 when compared to placebo ($p = .042$). Large variability in baseline scores prevented the assessment of severity scores and quality of life.

Concerning daily timing of disturbances, the majority of patients with IBS, up to 96% of them[7] complain of abdominal bloating (often ranked as their most bothersome symptom)[7,51,52] which characteristically varies in severity, increasing during the course of the day, with a sharp tendency to get worse after meals[7,8,9].

According to these data and to Kalman et al[29] evidence, stating that *Bacillus coagulans*-based probiotic product was effective and safe for abating abdominal pain and distention in the postprandial period, and bearing in mind that simethicone has an optimal antifoaming in the postprandial period[53], subjects in the present study were requested to take the tablet after meals. Most interesting clinical implication of present study is the significant improvement of IBS symptoms, with an optimal safety profile. In fact, simethicone is an inert substance, not absorbed into the bloodstream or from the gut lumen[40], which observed benefits are due only to local action, without any systemic effect of the compound[27]. It is well defined that probiotics help non-pathogenic bacteria against their pathogenic counterparts to compete for nutrient availability and for adhesion sites along the intestinal lumen, preventing both the overgrowth of pathogenic bacteria[29,54]. Specifically *Lactobacillus, Bifidobacteria*, and *Bacillus coagulans* are lactic acid producing bacteria, which can lower the pH, creating an environment that is not hospitable to many yeasts and bacterial species[55]. From a safety point of view *Bacillus coagulans* transiently occupies the gut for just a few days without repeated oral consumption[55].

Conclusions

In our knowledge this is the first randomized double-blind placebo-controlled clinical trial demostrating the efficacy and safety of a combi-

nation of simethicone and *Bacillus coagulans* in treatment of IBS. Further studies on a large population should be needed to confirm these preliminary data, but these findings can offer a safe and promising approach to treatment of IBS.

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Conflict of Interest Disclosure and Declaration of Funding Sources

The authors has no conflict of interest, financial conflicts to disclose and no financial interests in any products mentioned in this article.

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