A mixture of vegetable extracts (chamomile, passionflower, caraway, fennel) and enzymes (beta-galactosidase) for Irritable Bowel Syndrome (IBS): an observational study ("BIOVES")

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Summary. *Aims:* Irritable bowel syndrome (IBS) is a functional intestinal disorder. This syndrome may creates psychological disorders in patients who are affected and severely limits daily activities and lifestyle. *Methods:* We investigated the effect of the natural product consisting of chamomile, fennel, caraway, passionflower and melissa (*Spasmicol®*), on IBS patients. For the study, 187 patients with IBS, enrolled by primary care doctors, were treated with *Spasmicol® (Aristeia Farmaceutici s.r.l.)*, two tablets/daily, for 30 days. At the end of the study, patients were re-evaluated to analyse the effects of therapy. *Results:* After 30 days, patients showed a marked reduction of symptoms (abdominal pain, abdominal distention, stool habit changes). *Conclusions:* Due to to the combination of chamomile, fennel, caraway, melissa, passionflower and beta-galactosidase, the product *Spasmicol®* turned out to be remarkably effective in treating IBS symptoms.

Key words: irritable bowel syndrome, gastroenterology, supplements, alternative treatments

Introduction

Irritable bowel syndrome (IBS) is a functional intestinal disorder that affects 5% to 15% of the general population, moreso women than men (ratio 2:1). IBS is defined, according to Roma IV criteria, as the presence of recurrent abdominal pain on average at least 1 day per week during the previous 3 months (1-3). Furthermore, in order to make a correct diagnosis, the pain should be associated with at least two of the following symptoms or clinical signs:
- related to defecation;
- related to a change in evacuation frequency;
- related to a change in stool consistency.

These criteria have to be satisfied for at least the previous 3 months, while the onset of symptoms has to occur at least 6 months prior to diagnosis (1,2).

According to Roma IV criteria, IBS can be classified as follows:
- IBS that manifests itself mainly with constipation (IBS-C);
- IBS that manifests itself mainly with diarrhoea (IBS-D);
- Mixed type IBS (IBS-M), in which there is an alternation of diarrhoea and constipation;
- Unclassified IBS (IBS-U).

Stool classification is based on the Bristol Stool Scale (1,4).

IBS could be also classified as:
- sporadic IBS (or not specific IBS);
- post-infectious IBS (PI-IBS);
- IBS associated with Inflammatory Bowel Diseases (IBD) (IBD-IBS) (1,3,5).

The syndrome produces psychological disorders in patients who are affected and severely limits their lifestyle, as health-care utilization, and daily activities, such as work productivity, intimacy, leisure activities, interpersonal relationships, and eating habits.

Dietary measures may include fibre supplementation in order to improve the symptoms of constipation and diarrhoea; polycarbophil compounds (eg, Citrucel, FiberCon) to produce less flatulence than psyllium compounds (eg, Metamucil); judicious water intake, especially for those patients who predominantly experience constipation; caffeine avoidance in order to limit anxiety and symptom exacerbation; legume avoidance in order to decrease abdominal bloating. Lactose, fructose, and/or FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) should be limited or avoided in patients with these contributing disorders. Probiotics are being studied for their use in decreasing IBS symptoms (6).

Pharmacologic agents used for the management of symptoms in IBS include the following:
• Anticholinergics (eg, dicyclomine, hyoscyamine);
• Antidiarrheals (eg, diphenoxylate, loperamide);
• Tricyclic antidepressants (eg, imipramine, amitriptyline);
• Prokinetic agents;
• Bulk-forming laxatives;
• Serotonin receptor antagonists (eg, alosetron);
• Chloride channel activators (eg, lubiprostone);
• Guanylate cyclase C (GC-C) agonists (eg, linaclotide, plecanatide);
• Antispasmodics (eg, peppermint oil, pinaverium, trimebutine, cimetropium/dicyclomine);
• Altering bacterial flora and gas formation (eg, rifaximin).
In this open-label prospective observational study we aimed to investigate the clinical efficacy of *Spasmicol®*, a nature-derived dietary supplement which acts effectively in IBS patients, thanks to the synergistic combination of the following constituents:
– *Chamomile:* it has an anti-inflammatory effect COX–LOX dependent and antispasmodic, sedative and hypnotic effects (7);
– *Passionflower and Melissa*: they have a sedative effect mediated by the GABAergic system (8-10);
– *Melissa*: it adjusts the digestive processes thanks to its ability to moderate the frequency and the size of the slow intestinal waves, by doing so it has a myorelaxant effect (8,9);
– *Caraway and Fennel*: they reduce the mobility of the smooth intestinal muscle as a result of the release of acetylcholine (10,11);
– *Beta-galactosidase*: it increases the digestibility of lactose.

Materials and Methods

Despite the double-masked, randomized, placebo controlled, parallel-group trial is the gold standard for testing the efficacy of new treatments, we designed an open label, prospective observational study, due to the higher placebo rates found in European randomized controlled trials (RCTs) compared with those conducted in other continents, in trials evaluating antispasmodics, and in trials using shorter duration of therapy.

This prospective observational study involved primary care physicians (11 in total); each doctor recruited a maximum of 20 consecutive patients suffering from IBS. In the present study, 183 consecutive patients were recruited.

The patients were consecutively recruited and successively classified, according to Rome IV criteria, in IBS-C, IBS-D, IBS-M and IBS-U.

We excluded patients:
– with any alarm symptoms;
– with any unexplained weight loss;
– with any uninvestigated rectal bleeding;
– with past or present disease likely to complicate the evaluation of the study;
– with abdominal pain relieved by acid-inhibiting drugs;
– with pregnancy or lactation;
– with inability to complete the questionnaire;
– with family history of bowel cancer in a first or second-degree relative;

– with a recent (12 month) history of assumption of benzodiazepines, antidepressants, barbiturates, psychotropics, analgesics, prokinetics (cisapride, metoclopramide), bulk laxatives, antispasmodics, antidiarrhoeal agents, alternative medicines as herbal compounds.

We identified, accordingly:
– 76/183 patients with IBS-M;
– 40 patients with IBS-C;
– 40 patients with IBS-D;
– 24 patients with IBS-U.

In IBS-C patients, we evaluated, with a binary response (yes/no), if they have a satisfactory relief of their IBS symptoms during the past week (with particular attention to abdominal pain and altered bowel habits, considering in this case a complete spontaneous bowel movements (CSBM) per week superior to 3/week).

In IBS-D patients, we evaluated, with a binary response (yes/no):
– an assessment of stool consistency, by using the Bristol Stool Form Scale (a type 3 or 4 score was considered as a normalized consistency with a baseline type 5, 6 or 7 score);
– if they have a satisfactory relief of the abdominal pain, during the past week.

In IBS-M and IBS-U patients, we evaluated with a binary response (yes/no):
– if they have a satisfactory relief of the abdominal pain, during the past week;

– an assessment of stool consistency, by using the Bristol Stool Form Scale (a type 3 or 4 score was considered as a normalized consistency, with a baseline type 5, 6 or 7 score);
– if they have a complete spontaneous bowel movements (CSBM) per week greater than 3/week.

All the patients were treated with a daily oral intake of *Spasmicol*® 500 mg (Aristeia farmaceutici s.r.l., Valguarnera, Italy). The chewable tablets were administered two times daily, before the main meals, for 30 days. All the patients were re-evaluated at the end of the study (t_1). Four patients (2.1%, 2 females) were discarded due to their scarce adherence to therapy (they did not take the drug constantly).

Finally, safety was also assessed, while quality of life was not assessed.

Table 1 and 2 shows bowel habits variations and pain relief, respectively, after 30 days of treatment with *Spasmicol*®.

Data were reported as percentages for categorical variables and as means (95% confidence intervals) for quantitative variables. The comparison between groups (t_0 versus t_1) was performed using the non-parametric Pearson chi-square test. Stata (StataCorp. 2016. Stata Statistical Software: Release 14.1. College Station, TX: StataCorp LP) was used for database management and analysis.

Table 1. Bowel habits variations pre and post treatment with Spasmicol®

Subtypes of irritable bowel syndrome at t_0 (number of cases/ total of patients)	Responders according to bowel habits at t_1 (number of cases/ total of patients)
IBS-M	76/183	45/183
IBS-C	40/183	25/183
IBS-D	43/183	31/183
IBS-U	24/183	15/183

Table 2. Pain relief pre and post treatment with Spasmicol®

Subtypes of irritable bowel syndrome at t_0 (number of cases/ total of patients)	Responders according to abdominal pain relief at t_1 (number of cases/ total of patients)
IBS-M	76/183	56/183
IBS-C	40/183	30/183
IBS-D	43/183	22/183
IBS-U	24/183	16/183

Results

In the present study, 183 consecutive patient were recruited (55 male [29.4 %] and 132 female patients), ranging from 18 to 80 years (mean: 50.2 years).
After 30 days of treatment:

– 45 out of 76 IBS-M patients reported a normalized stool consistency, with a complete spontaneous bowel movements (CSBM) per week greater than 3/week, however with 20 out 76 not showing satisfactory relief of the abdominal pain;

– 25 out of 40 IBS-C patients reported a complete spontaneous bowel movements (CSBM) per week superior to 3/week, however with 10 out of 40 a satisfactory relief of the abdominal pain;

– 31out of 43 IBS-C patients reported a normalized stool consistency, however with 11 out of 43 not showing a satisfactory relief of the abdominal pain;

– 16 out of 20 IBS-U patients reported a normalized stool consistency , with a complete spontaneous bowel movements (CSBM) per week greater than 3/week, however with 9 out of 20 not showing satisfactory relief of the abdominal pain.

Significant severe, moderate or mild adverse events were not reported by the enrolled patients. The statistical analysis showed that the scores relative **to stool habits and abdominal pain resulted significantly different** (p < 0.001 and p = 0.002 respec-

tively) between the considered observational points (t_0 and t_1).

For the parameter "abdominal distension" the difference was not statistically significant (p = 0.116), but this consideration could be biased by the great subjectivity of this parameter.

Discussion

Despite the costs and numerous investigations into the pathophysiology and treatment of this disorder, our understanding of IBS is still incomplete. Over the last ten years, increasing insight into the enteric nervous system and how its dysfunction may play a role in IBS pathology has emerged. Additionally our increasing understanding of the gut microbiome and how its potential disruption may lead to IBS symptoms has also been highlighted (12-17). Currently, many clinicians use a treatment approach based on the predominant symptoms of the patient: constipation (IBS-C), diarrhoea (IBS-D), or mixed symptoms (IBS-M). Medications that relax smooth muscle *via* anticholinergic mechanisms or calcium channel antagonism have been commonly utilized for the treatment of IBS. Among these are alverine, dicyclomine (with or without cimetropium), hyoscyamine, otilonium, pinaverium, scopolamine, and trimebutine. Generally, antispasmodics have been utilized for their effects on gastrointestinal motility in attempts to reduce abdominal pain associated with IBS. Some of them could improve IBS symptom scores and global assessment. Unfortunately, anticholinergic side effects of these agents often include dose-related vision disturbances, dry mouth, and dizziness. Moreover, antispasmodics can also cause constipation, thus they should be used cautiously in patients with IBS-C.

In this study we have chosen open label, prospective observational design, due to the higher placebo rates found in European randomized controlled trials (RCTs) compared with those conducted in other continents, in trials evaluating antispasmodics, and in trials using shorter duration of therapy; in spite of this factor, the double-masked , randomized, placebo controlled, parallel-group trial is the gold standard for testing the efficacy of new treatments in IBS.
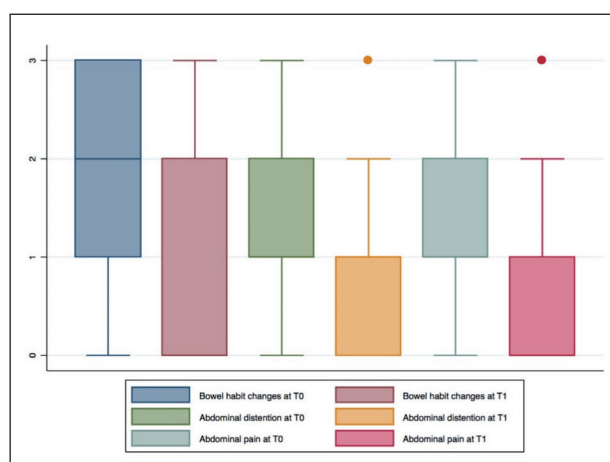

Figure 1. *The Box and Whisker Plot chart* highlights the difference in distribution (regarding median and interquartile distance) of the scores above t_0 and t_1, and underlines the presence of outliers in abdominal distension and abdominal pain, observed at t_1.

The placebo effect in clinical trials has long been known, and because of the vague nature of IBS symptoms and the use of primary outcomes that are often subjective in nature, high placebo response rates have been noted in IBS trials. However, Kim et al. (18) have also described the potential for a "pre-cebo" effect in IBS, which impacts the treatment outcome even before the study begins. The pre-cebo effect describes the impact of consent language used in clinical trials on expectations of benefit from the study medication.

The obtained results showed a marked reduction of IBS symptoms, according to *Roma IV criteria*. The remission or reduction of symptoms related to the disease could be identified into the synergistic activity of the principles contained in the product. They have shown their ability to reduce abdominal pain by increasing the digestibility of lactose, thanks to an anti-inflammatory effect on the intestinal mucosa, by relaxing the intestinal smooth muscles, reducing bowel gas formation, and modulating and regulating intestinal motility.

Conclusions

The combined action of chamomile, fennel, caraway, melissa, passionflower and beta-galactosidase, demonstrated potentially beneficial effects on all physiopathological components of IBS, improving patients' quality of life, without important side effects. *Spasmicol*® has been found to exert beneficial effects for patients with IBS. The product regularizes bowel movements, reducing or eliminating diarrhoea or constipation, reducing the formation of intestinal gases and decreasing or eliminating intestinal distention; it also reduces or even eliminates abdominal pain thanks to the triple synergistic effect of its main components (anti-inflammatory, improvement of lactose digestibility, spasmolytic).

Acknowledgments

Conflicts of interest

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