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Supplementation with a lecithin-based delivery form of *Boswellia serrata* extract (Casperome®) controls symptoms of mild irritable bowel syndrome

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Abstract. – OBJECTIVE: Irritable Bowel Syndrome (IBS) is a chronic, gastrointestinal disorder in which abdominal pain or discomfort is associated with defecation or changes in bowel habits. Its multifactorial pathophysiology leads to a variety of available treatments, mainly aimed at controlling symptoms. The management of IBS patients could be optimized by individualized strategies, including non-pharmaceutical approaches. In this study, we evaluated the efficacy and safety of a novel delivery form of *Boswellia serrata* extracts (BSE) (Casperome®) in patients with IBS.

PATIENTS AND METHODS: 71 otherwise healthy subjects with idiopathic IBS were recruited. Participants were assigned to the following management strategies: hyoscine butylbromide; papaverine hydrochloride + *A. belladonna* extract; supplementation with Casperome®. Predominant IBS symptoms were evaluated at inclusion and at the end of the observational period (4 weeks). The numbers of subjects who needed rescue medication or medical attention/hospital admission were recorded. Adverse events were also evaluated.

RESULTS: In all groups, the IBS symptoms investigated, namely abdominal pain, altered bowel movements, meteorism and cramps improved during the observational period. Of note, the number of subjects who needed medical attention significantly decreased only in Casperome®-supplemented group. In addition, Casperome® supplementation was related to a lower incidence of side effects (mainly stypsis).

CONCLUSIONS: This preliminary study suggests that Casperome® supplementation could represent a promising alternative approach to manage symptoms associated with IBS in otherwise healthy subjects.

Key Words:
Irritable bowel syndrome, Diarrhea, Abdominal pain, *Boswellia serrata* extracts, Phytosome.

Introduction

Irritable Bowel Syndrome (IBS) is a chronic, relapsing, gastrointestinal disorder in which abdominal pain or discomfort is associated with defecation or changes in bowel habits. Diagnostic criteria based on clinical findings include recurrent abdominal pain or discomfort for at least 3 days per month in the last 3 months, associated with two or more of the following: improvement with defecation, onset associated with a change in stool form or stool frequency[1]. According to the predominant bowel habit, IBS can be subclassified in diarrhea predominant (IBS-D), constipation predominant (IBS-C), mixed subtype (IBS-M) or unclassified (IBS-U)[2]. The pathogenesis of IBS is complex, heterogeneous and incompletely understood; during the last decades, a number of factors including genetic/social learning factors, diet, intestinal microbiota and low-grade chronic intestinal inflammation, have been associated with IBS pathophysiology[3-6]. The development of long-lasting gastrointestinal symptoms after acute gastroenteritis supports a role for the inflammatory factors[7]. In addition, an increased innate immune activity in the intestinal mucosa and in blood has been observed in subpopulations of patients with IBS[7]; in particular, an increased

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number of mast cells in both colon and upper gastrointestinal tract was the most common abnormality observed in IBS patients[8].

The multifactorial pathophysiology of IBS explains to the wide variety of available treatment strategies, mainly aimed at controlling the predominant symptoms. Effective pharmacological therapies for IBS include: antidiarrheal medications such as loperamide; 5-HT3 receptor antagonists that influence gastrointestinal motility and visceral sensation; antispasmodics, namely drugs with anticholinergic or calcium channel blocking properties (otilonium, hyoscine, cimetropium, pinaverium, and dicyclomine); probiotics and antibiotics to modify the gut microbiota; antidepressants[9,10]. However, most of IBS patients do not respond to, or become dissatisfied with conventional therapies probably because of the related side effects. Management of subjects with IBS could be optimized by individualized, non-pharmaceutical approaches that include dietary, lifestyle, and behavioral interventions[11,12]. Herbal remedies could also represent complementary alternative strategies for the management of gastrointestinal disorders such as IBS[13]. Recently, several studies explored the effects of supplementation with *Boswellia serrata* extracts (BSE) in inflammatory bowel diseases, namely ulcerative colitis[14-16], and Crohn's disease[17,18]. These beneficial effects could be mainly attributed to the active constituents of BSE, namely boswellic acids, that are able to modulate the immune system in different ways, as demonstrated by *in vitro* and *in vivo* studies[19-21].

In this registry study, we aimed at evaluating the efficacy and safety of the novel delivery form of BSE (Casperome®) in subjects with IBS.

Patients and Methods

In this registry, supplement study, 71 otherwise healthy subjects with idiopathic IBS were recruited. Previous endoscopic evaluation by colonoscopy or colon capsule endoscopy (PillCam colon capsule endoscope)[22] performed at inclusion showed normal intestinal walls and no significant anatomical or pathological abnormalities. The affected subjects had no previous abdominal or gynecological surgery. Other conditions including endometriosis, abdominal epilepsy, alterations in intestinal perfusion were excluded. Fecal exams had excluded intestinal parasites and possible food intolerance. Occult blood and calprotectin level in stools were negative at inclusion. Considering the occurrence of abdominal pain episodes (8-14 episodes/month) in the participants at inclusion, the IBS could be defined as sporadic. Bowel activity was generally normal (or with minor alterations) without constipation or diarrhea. No remarkable weight loss was reported in the previous months. Supplement studies define the field of activity of pharma-standard supplements and their possible preventive, pre-therapeutic applications.

"Supplement studies" produce supplementary data to be compared with those from the best available management plans. These type of studies are performed using pharmaceutical standard supplements with high level of safety and standardization[23-25] considering safety and tolerability as the first items.

Participants (n = 71) decided to follow one of these management strategies:

Group 1: Hyoscine butylbromide (Buscopan®), administrated when needed;
Group 2: Papaverine hydrochloride 10 mg + belladonna (*A. belladonna)* extract 10 mg, namely Antispasmina colica®, administrated when needed;
Group 3: Supplementation with a lecithin-based delivery form of BSE (Casperome®), the dosage scheme was 1 tablet of 250 mg per day, for 4 weeks.

Conventional drugs were considered as rescue medications in case the Casperome® supplementation failed to control and/or alleviate IBS symptoms.

The following IBS symptoms were evaluated by subjects during the week before inclusion and during the week before the end of the observational period (4 weeks):

Abdominal pain: episodes were classified with an analogue scale of pain ranging from 1 (no pain) to 4 (continuous and severe pain);

Altered bowel movements: episodes were classified with an arbitrary scale ranging from 1 (no movements) to 4 (continuous and severe movements);

Meteorism: episodes were classified with an arbitrary scale ranging from 1 (no episodes) to 4 (very frequent episodes);

Cramps: episodes were classified with an arbitrary scale ranging from 1 (no episodes) to 4 (very frequent episodes).

We also reported the number of patients who experienced any previously described symptoms

Table I. Demographic details of the study population. SD: standard deviation.

	Group 1 (hyoscine butylbromide)	Group 2 (papaverine hydrochloride + belladonna extract)	Group 3 (Casperome® supplementation)
Subjects (female)	24 (13)	23 (14)	24 (16)
Age, years (mean ± SD)	36.0 ± 3.0	35.3 ± 4.0	35 ± 2.4
Days of follow up	31.2; 2.2	32.2.2	31-.4; 2.3

during the study. The number of subjects who needed rescue medication as well as the number of subjects who needed medical attention or hospital admission were recorded. Basic blood tests and fecal examination were performed before and after the observational period. Treatment tolerability and adverse events were also evaluated.

Statistical Analysis

Intragroup comparisons were performed by using ANOVA test with post-hoc Bonferroni correction. p-value < 0.05 was considered statistically significant.

Results

Demographic details of the study population are shown in Table I. All groups were comparable in term of age and gender distribution and for lenght of follow up. The groups presented also similar clinical characteristics at inclusion (Table II). All IBS symptoms investigated, namely abdominal pain (Figure 1 and 2), altered bowel movements, meteorism and cramps (Table II) improved during the observational period, with each management strategy.

The number of subjects with any IBS symptoms significantly decreased after the observational period only in Casperome®-supplemented group (Table II). Consistently, in supplemented group (group 3) also the number of patients who needed medical attention significantly decreased during the study (Table II).

The prevalence of side effects was significantly higher in IBS patients treated with pharmacological options, 28% for group 1 (hyoscine butylbromide) and 26% for group 2 (papaverine hydrochloride + belladonna extract), compared to Casperome®-supplemented subjects (8,2%).

In addition, the most frequent reported side effect was stypsis, that was associated with nausea in 2 hyoscine butylbromide®-treated patients, and with nausea and headache in 4 papaverine hydrochloride + belladonna extract-treated patients.

In IBS patients supplemented with Casperome®, mild stypsis was the only unwanted effect recorded. Two subjects with ISB symptoms managed by conventional, pharmacological options (group 1 and group 2) experienced a mild, transient hypotension, possibly linked to the treatment.

Routine blood test and fecal exams were normal at inclusion and at 4 weeks.

Table II. Evaluation of symptoms associated with IBS and need for additional medication and medical attention.

	Group 1 (hyoscine butylbromide)		Group 2 (papaverine hydrochloride + belladonna extract)		Group 3 (Casperome® supplementation)	
	0 week	4 week	0 week	4 week	0 week	4 week
Altered bowel movements (range 1-4)	2.2 ± 0.2	2.0 ± 0.3	2.4 ± 0.3	1.3 ± 0.2*	2.1 ± 0.2	1.1 ± 0.1*
Meteorism (range 1-4)	3.1 ± 0.5	2.4 ± 0.3*	3.0 ± 0.3	2.3 ± 0.2*	2.9 ± 0.3	1.2 ± 0.3*
Cramps (range 1-4)	3.2 ± 0.3	1.1 ± 0.2*	3.3 ± 0.3	1.0 ± 0.2*	3.2 ± 0.2	1.1 ± 0.1*
ISB symptoms, n. of patients (%)	13 (54.1)	5 (20.8)	12 (52.1)	6 (26.0)	14 (58.0)	3 (12.5)*
Need for additional drugs, n. of patients (%)	–	2 (8.3)	–	2 (8.7)	–	2 (8.3)
Need for medical attention, n. of patients (%)	–	3 (12.5)	–	3 (13.0)	–	1 (4.1)º

Data are reported as mean ± standard deviation; *p < 0.05 *vs*. baseline; ºp < 0.05 *vs*. the other groups.

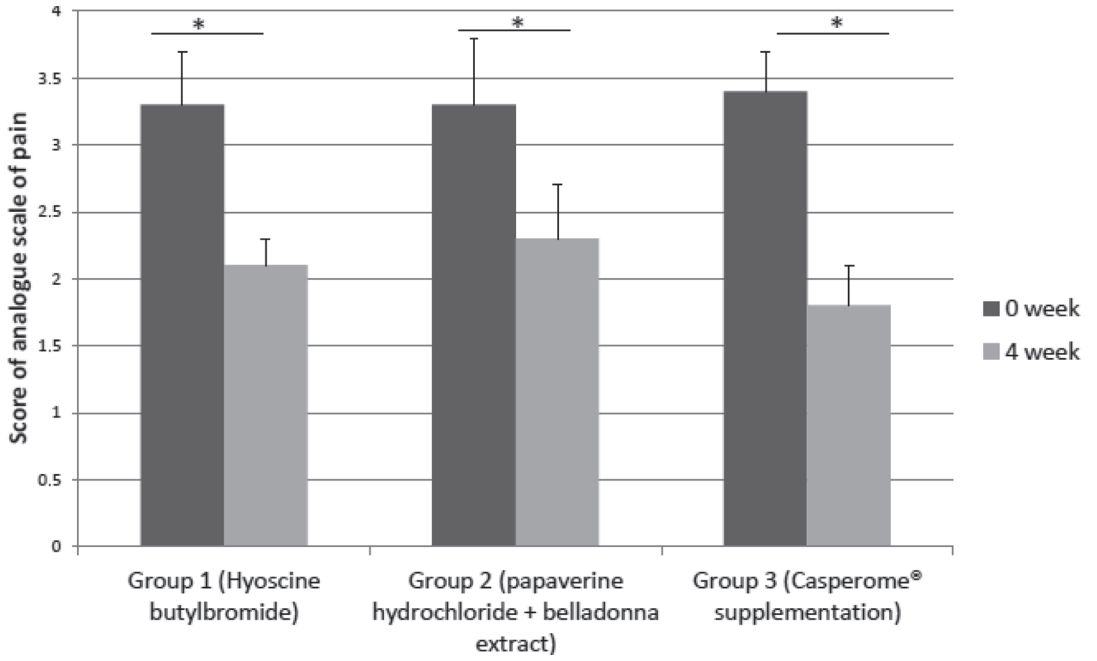

Figure 1. Recurrent abdominal pain.

Discussion

The prevalence of IBS varies by geographic region, ranging between around 10% and 25% of the adult population, with the lowest occurring in South Asia (7.0%) and the possibly, the highest frequency reported in South America (21.0%)[26]. Prevalence of non-life-threatening conditions is greatly affected by reporting. Many, non-developed nations may have a large percentage of subjects with intestinal parasites. Globally, IBS may affect around 11% of the worldwide pop-

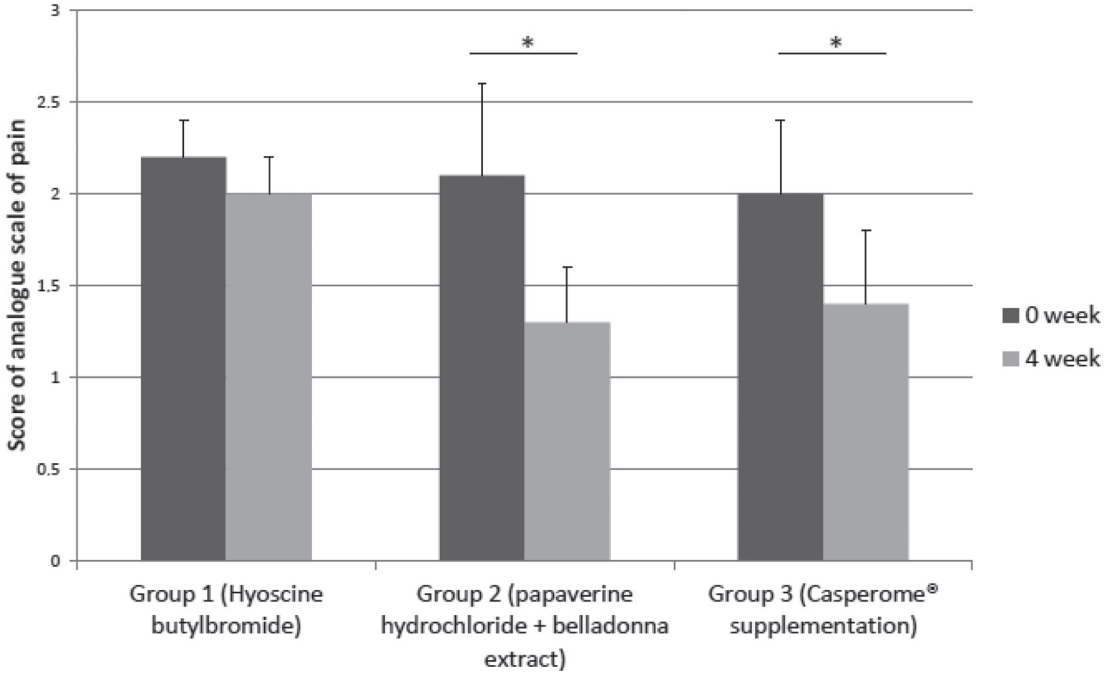

Figure 2. Abdominal pain at pressure.

ulation[26]. However IBS is often unrecognized or untreated and only 25% of subjects with IBS symptoms consult physicians[27]. Despite that a minority of IBS patients seek professional healthcare, the cost of this condition may be high. In 2000, the total direct costs of IBS were 1.7 billion dollars, whereas the indirect costs were 20.2 billion dollars, in USA[28]. Moreover, IBS substantially impacts on patients' work and social life, reducing their quality of life (QoL). Considering the chronic nature of this complex disorder, patients would sacrifice 10-15 years or more of their remaining life expectancy for an immediate cure[29]. The use of supplements and self-prescription, when the medical issue is well-diagnosed and of mild intensity, could reduce costs and side effects.

IBS is associated with relevant social and economic costs to patients in term of impaired QoL, healthcare systems; new 'soft' and safer supplementary interventions to effectively manage IBS symptoms are now possible. In particular, greater consideration of supplementary interventions is advisable.

Several supplementary interventions have been shown to be effective and safe in IBS management[30], including plant-derived pharma-standard products[31].

In vitro and *in vivo* studies demonstrated that BSE directly inhibited intestinal motility with a mechanism involving L-type Ca^{2+} channels, preventing experimental diarrhea in animal models, without slowing the rate of transits[32]. Notably, we showed that the lecithin-based delivery form of BSE (Casperome®) attenuated symptoms associated with mild ulcerative colitis in remission, including intestinal pain, diarrhea episodes and cramps[14]. The combination of standardized BSE with lecithin remarkably increased its bioavailability and penetration across biological membranes[33], two features that strengthen the potential effectiveness of BSE in IBS. In this registry, supplement study we observed that Casperome® supplementation rapidly alleviated IBS symptoms.

However, differently from pharmacological options, Casperome® supplementation is associated with a lower incidence of side effects (mainly stypsis). In addition, no alterations of gut microbiota – as assessed by examination of feces – were reported.

Larger studies in in a wider populations – with a wider distribution of signs/symptoms and for longer periods – are in progress.

Conclusions

This preliminary study suggest that Casperome® supplementation could represent a promising alternative approach to manage symptoms associated with IBS in otherwise healthy subjects.

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Conflict of Interest

ST and AR are employees of Indena S.p.A. LG is a consultant of Indena S.p.A.

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