Original article

doi:10.1111/j.1463-1318.2012.03152.x

Microencapsulated sodium butyrate reduces the frequency of abdominal pain in patients with irritable bowel syndrome

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Received 27 February 2012; accepted 1 May 2012; Accepted Article online 27 June 2012

Abstract

Aim Abdominal pain, defaecation disorder and change of bowel habit are the commonest symptoms of irritable bowel syndrome (IBS). The effect of microencapsulated sodium butyrate (MSB) was assessed on the severity of symptoms in patients with IBS.

Method Sixty-six patients treated with one of the standard pharmacological therapies for at least 3 months were included in the study. They were randomized to receive MSB as a supplemental treatment to standard therapy or to receiving a placebo. Previous pharmacological therapy was continued throughout the study in both arms. Clinical evaluation was performed at baseline, 4 and 12 weeks. Each assessment was documented by a validated visual analogue score questionnaire measuring the severity of selected clinical symptoms, a closed-end questionnaire measuring the frequency of selected clinical symptoms and a single closed-end question measuring the subjective improvement of symptoms.

Results After 4 weeks there was a significant decrease of pain during defaecation in the MSB group which extended to improvement of urgency and bowel habit at 12 weeks. Reduction of abdominal pain, flatulence and disordered defaecation was not statistically significant.

Conclusions MSB as a supplemental therapy can reduce the frequency of selected clinical symptoms in patients with IBS, without significant influence on reducing symptom severity.

Keywords Irritable bowel syndrome, abdominal pain, defaecation disorders, sodium butyrate

What is new in this paper?

Therapies available to patients with irritable bowel syndrome are often suboptimal. Sodium butyrate as a supplemental agent to a standard pharmacological therapy can decrease the frequency of irritable bowel syndrome clinical symptoms.

Introduction

Irritable bowel syndrome (IBS) is one of the most common disorders, occurring in 10–30% of the general population [1–4]. The main symptoms include disordered defaecation, change in bowel habit and abdominal pain [5,6]. Modification of diet, psychotherapy and change in lifestyle may be currently advised [6].

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Evidence based treatment of constipation-predominant IBS include lubiprostone and tegaserod. In the treatment of the diarrhoea-predominant form evidence based therapies include non-absorbable antibiotics (rifaximin), alosetron and probiotics. Other commonly used treatments include antispasmodics and antidepressants. Complementary therapies and alternative medicine therapies consist of other probiotic agents, herbal remedies and acupuncture. Unfortunately the wide array of therapeutic approaches results in only 7–15% advantage over placebo [7]. Ongoing research is focusing on new treatments such as pancrealipase [8], linaclotide [9], *Lactobacillus* LB [5] or butyrate [10].

Sodium butyrate (SB) is an important energy substrate for colonocytes. In experimental models involving malignant cells apoptosis-stimulating properties of SB have been demonstrated and it may have the potential to induce visceral hypersensitivity without altered pathology. Several clinical studies report reduction of visceral pain in IBS patients taking SB [11]. An anti-inflammatory and trophic effect of SB can be beneficial for patients with inflammatory bowel diseases, diverticulosis and diverticulitis, diarrhoea due to other causes, cachexia and malabsorption [12,13]. In the present study we have evaluated the effect of microencapsulated SB (MSB) on the severity and frequency of abdominal pain and associated symptoms in patients with IBS.

Methods

The study was performed as a parallel, double-blinded, randomized, placebo-controlled per-protocol clinical study, in accordance with the Helsinki Declaration and the regulations of the Ethics Committee of Poznan University of Medical Sciences (26/11). Patients were recruited from two outpatient coloproctology clinics.

Of 108 patients potentially eligible 29 were excluded because they did not fulfil the entry criteria of the study. Seventy-nine patients were randomized to receive MSB (Debutir®; Polfa Łódź, 91-002 Łódź, Poland) in a dose of 300 mg per day (2 × 150 mg) and to a placebo group. Placebo was identical in size and shape. In the same capsule the neutral for the health compound was included. Both groups were allowed to continue their previous pharmacological therapy. A questionnaire recording symptoms occurring within the last week was completed at each clinic visit at baseline and at 4 and 12 weeks after the start of treatment. Thirteen patients were unable to cooperate with the protocol and were excluded. A total of 66 patients (42 women) were included in the analysis (Fig. 1).

Patients with IBS qualified for entry if they experienced symptomatic IBS despite current drug treatment and wished to supplement their therapy with an additional therapeutic agent. The inclusion criteria were age (19–65 years), lack of organic large bowel disease (normal colonoscopy or radiological studies), presence of gastrointestinal symptoms suggestive of IBS (Rome III criteria regardless of its subtypes) and continued pharmacotherapy with one or more agents for at least 3 months before the study. The exclusion criteria were acute inflammation within the last 2 weeks (fever, leucocytosis), previous abdominal surgery (except appendectomy and hernia repair), history of IBD, pharmacotherapy with antibiotics or probiotics within 2 weeks of the study, current psychiatric disease, severe comorbidity, pregnancy and breast-feeding. To avoid bias by dietary changes or tertiary pharmacological agents the patients were asked not to implement any dietary changes or use any additional pharmacological treatment throughout the study period.

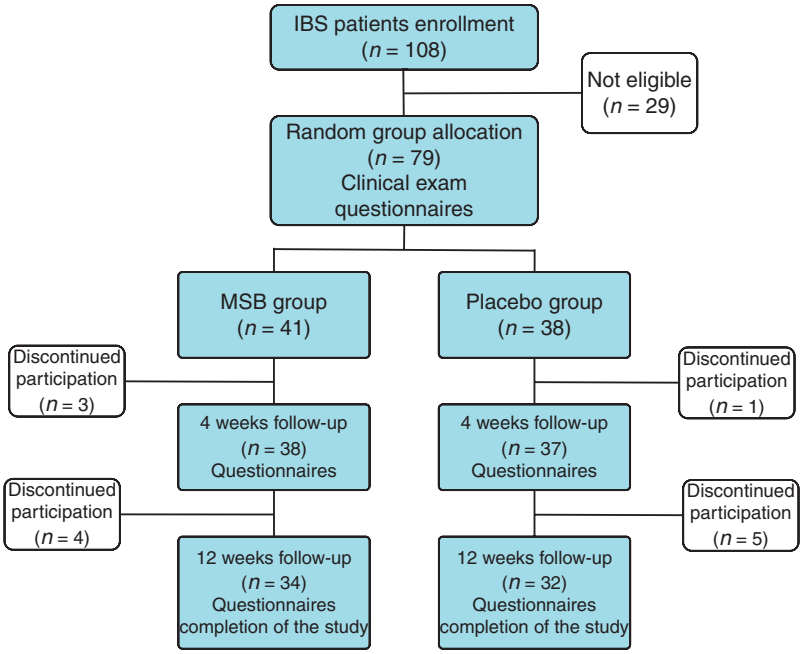

Figure 1 A flowchart representing the course of the randomized double-blinded clinical study of MSB in patients with IBS.

Symptom severity was evaluated using several questionnaires. The Visual Analogue Scale for IBS (VAS-IBS) focuses on intensity of IBS symptoms occurring within the last week using a 0–10 scale, where zero corresponds to the smallest and 10 the highest symptom intensity [11]. The specific elements measured by the VAS-IBS are abdominal pain, bloating with flatulence and dysfunctional defaecation. The VAS-IBS scale is a commonly accepted and validated tool for comparison of IBS symptom intensity [14].

Frequency of IBS symptoms was assessed with a closed-end question (yes or no) regarding occurrence of a specific symptom within the previous week. Patients reported whether within the last week the following symptoms occurred: spontaneous abdominal pain, postprandial abdominal pain, abdominal pain at defaecation, urge sensation after defaecation, presence of mucus in stool, stool consistency change, defaecation difficulties (constipation).

To assess subjective change of symptoms, patients were asked a single closed-end question requiring a yes or no answer: 'Did you observe adequate relief of irritable bowel syndrome symptoms related to abdominal pain or discomfort within the past week?' At baseline the VAS-IBS questionnaire and the frequency of symptoms questionnaire were completed. All three questionnaires were also completed by patients at 4 and 12 weeks (Fig. 1).

Statistical analysis

Statistical analysis included median and interquartile range (Q25 and Q75) measuring the degree of dispersion and functioning as the median deviation. Additionally mean values with standard deviation were calculated. The differences between the groups were analysed with the non-parametric Mann–Whitney test and the Kruskal–Wallis test with the Dunn test (*post hoc* test). A probability value of $P < 0.05$ was considered significant.

Results

The MSB group ($n = 34$) and the placebo control group ($n = 32$) did not differ significantly in age, clinical symptom severity, disease duration and type of symptoms. Both groups had a higher percentage of women. The most frequently administered drugs used before the study were mebeverine ($n = 19$ MSB group, $n = 20$ control group), trimebutine ($n = 19$ MSB group, $n = 20$ control group) and bulk-producing agents and lubricants ($n = 20$ MSB group, $n = 17$ control group). Other therapies included simethicone ($n = 13$ MSB group, $n = 16$ control group) and loperamide ($n = 14$ MSB group, $n = 15$ control group). No significant differences in type of drug were noted.

There were no adverse effects in either arm of the study. There was a trend towards a gradual decrease of intensity of pain symptoms, intensity of bloating and intensity of dysfunctional defaecation in the MSB group. This did not, however, reach statistical significance. Values at 4 and 12 weeks are shown in Table 1.

At 4 weeks there was a statistically significant decrease in frequency of abdominal pain during defaecation ($P = 0.0032$) and a non-statistically significant trend towards a decrease in frequency of postprandial pain ($P = 0.0968$). At 12 weeks there was a statistically

Table 1 Assessment of severity of selected symptoms in the week before the visit (VAS-IBS scale).

	MSB ($N = 34$)			Placebo ($N = 32$)			
	Mean	SD	Median	Mean	SD	Median	*P*
Study begins							
VAS abdominal pain	4.65	2.90	4.50	4.88	2.67	4.50	ns
VAS bloating with flatulence	3.91	1.60	4.00	3.66	1.58	3.50	ns
VAS dysfunctional defaecation	3.74	1.66	4.00	3.81	1.40	3.50	ns
After 4 weeks of study							
VAS abdominal pain	4.41	2.90	4.00	4.94	2.56	4.50	ns
VAS bloating with flatulence	3.65	1.74	3.00	3.75	1.76	3.50	ns
VAS dysfunctional defaecation	3.41	1.76	3.00	3.88	1.62	4.00	ns
After 12 weeks of study							
VAS abdominal pain	3.88	3.06	3	4.97	2.73	5	ns
VAS bloating with flatulence	3.26	2.11	3	3.78	2.09	4	ns
VAS dysfunctional defaecation	3.06	2.10	3	3.94	2.06	4	0.0598

ns, not significant.

significant decrease in frequency of spontaneous abdominal pain, postprandial abdominal pain, abdominal pain during defaecation and urge after defaecation and an improvement in constipation. At 12 weeks the frequency of all measured parameters decreased (Table 2, Fig. 2).

Subjective changes of symptoms measured with a single closed-end question (yes or no answer) 'Did you observe adequate relief of irritable bowel syndrome symptoms related to abdominal pain or discomfort within the past week?' showed that the MSB group had statistically significant relief of symptoms both at 4 weeks and at 12 weeks (Table 3).

Discussion

There are various theories regarding the mechanism of abdominal pain in IBS. It is frequently assumed that it is related to abnormalities in digestion, fermentation and excess amount of gases leading to bloating and mechanical distension of the intestinal wall. The exact pathogenesis is not fully understood and is subject to ongoing investigation. A recent study by Bulmer and Grundy [15] indicates that the visceral pain in IBS can be caused by abnormalities of neuronal transmission, especially its excessive activation. Another cause might involve elevated levels of brain-derived neurotrophic factor. Changes associated with the ultrastructure of nerve fibres located in mucous membranes and oedema of intracellular structures with emphasis on mitochondrial changes are also reported to be relevant [16]. Moreover, an association of pain symptoms with central nervous system function has been assessed in 'mindfulness-based treatment'. The efficacy of this treatment was comparable to pharmacological treatment proving that a considerable component of this syndrome can be psychological [17].

The role of SB on the intestine and its direct action on intestinal mucosa have been investigated previously. SB is one of the essential elements of intestinal haemostasis, crucial for the natural processes of regeneration and replacement of intestinal epithelium. A number of

Table 2 Frequency of symptoms in the week before the visit.

	MSB (N = 34)			Placebo (N = 32)			
	Mean	SD	Median	Mean	SD	Median	P
Baseline							
Spontaneous abdominal pain	0.53	0.51	1	0.53	0.51	1	ns
Postprandial abdominal pain	0.44	0.50	0	0.44	0.50	0	ns
Abdominal pain during defaecation	0.35	0.49	0	0.56	0.50	1	ns
Urge sensation after defaecation	0.26	0.45	0	0.38	0.49	0	ns
Mucus in stool	0.15	0.36	0	0.13	0.34	0	ns
Changes in stool consistency	0.44	0.50	0	0.38	0.49	0	ns
Constipation	0.38	0.49	0	0.47	0.51	0	ns
After 4 weeks of study							
Spontaneous abdominal pain	0.382	0.493	0	0.50	0.51	0.5	ns
Postprandial abdominal pain	**0.324**	**0.475**	**0**	**0.56**	**0.50**	**1**	**0.0968**
Abdominal pain during defaecation	**0.176**	**0.387**	**0**	**0.59**	**0.50**	**1**	**0.0032**
Urge sensation after defaecation	0.235	0.431	0	0.41	0.50	0	ns
Mucus in stool	0.088	0.288	0	0.13	0.34	0	ns
Changes in stool consistency	0.382	0.493	0	0.41	0.50	0	ns
Constipation	0.353	0.485	0	0.47	0.51	0	ns
After 12 weeks of study							
Spontaneous abdominal pain	**0.21**	**0.41**	**0**	**0.50**	**0.51**	**0.5**	**0.0132**
Postprandial abdominal pain	**0.21**	**0.41**	**0**	**0.56**	**0.50**	**1**	**0.0031**
Abdominal pain during defaecation	**0.15**	**0.36**	**0**	**0.59**	**0.50**	**1**	**0.0002**
Urge sensation after defaecation	**0.15**	**0.36**	**0**	**0.44**	**0.50**	**0**	**0.0100**
Mucus in stool	0.12	0.33	0	0.22	0.42	0	ns
Changes in stool consistency	**0.18**	**0.39**	**0**	**0.41**	**0.50**	**0**	**0.0417**
Constipation	**0.24**	**0.43**	**0**	**0.47**	**0.51**	**0**	**0.0493**

ns, not significant.

There were no adverse effects in either arm of the study. Values are shown as proportions.

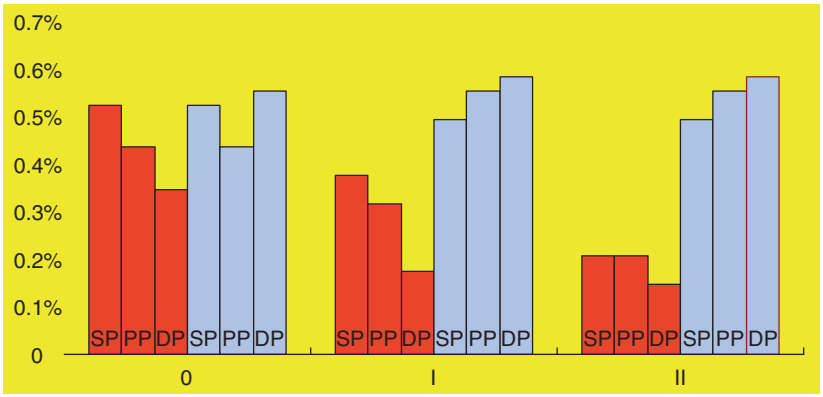

Figure 2 Change in frequency of abdominal symptoms in the MSB and placebo control groups. Values on the *x* axis represent patient visits (0 initial visit, I 4-week visit, II 12-week visit). Values on the *y* axis represent the percentage of patients reporting the symptom expressed as a proportion of the whole group. The red and grey columns represent the prevalence of symptoms in the MSB group and the placebo group. SP, spontaneous abdominal pain; PP, postprandial abdominal pain; DP, pain on defaecation.

Table 3 Subjective assessment of changes of abdominal pain estimated by a single closed-end question (yes or no answer): 'Did you observe adequate relief of irritable bowel syndrome symptoms related to abdominal pain or discomfort within the past week?'

	MSB ($N = 34$)		Placebo ($N = 32$)		
	Number of patients	Percentage of study group	Number of patients	Percentage of study group	*P*
After 4 weeks of study					
Patients reporting subjective relief in IBS symptoms YES	**11**	**32**	**2**	**6.25**	**<0.01**
After 12 weeks of study					
Patients reporting subjective relief in IBS symptoms YES	**18**	**53**	**5**	**15.6**	**<0.01**

pathological processes involving the large intestine can be associated with diminished endogenous butyric acid levels [18]. The results of the present study showing that MSB decreases the frequency of IBS symptoms may be associated with decreasing oversensitivity of intestinal receptors leading to a decreased amplitude of intraintestinal pressure [17]. SB can also improve the efficacy of peristalsis of the large intestine circular muscle resulting from changes in intestinal neurotransmitters, especially decreased peristaltic activity [18].

Several disease-specific questionnaires have been used to evaluate gastrointestinal symptoms in IBS patients. Most are very time-consuming for the patient, which can be a serious limitation in daily clinical practice. With the introduction of VAS-IBS clinicians have gained a validated comparable tool consisting of a short questionnaire suitable for clinical practice [15]. A single additional closed-end question 'Did you observe adequate relief of irritable bowel syndrome symptoms related to abdominal pain or discomfort within the past week?' can be a valuable tool in the subjective assessment of the efficacy of a treatment and the degree of patient satisfaction. Utilizing validated questionnaires to assess the effectiveness of treatment allows comparison of the outcome [19,20].

The present study demonstrates that administration of SB in microencapsulated form significantly reduces some of the symptoms of IBS especially at 12 weeks of treatment. To the best of our knowledge this is the first study to evaluate the microencapsulated form of SB. When administered not in capsular form, SB is subject to rapid ingestion in the upper digestive tract. The microencapsulated formulation prevents it from being ingested early, resulting in more targeted treatment in the more distal intestine.

With regard to symptoms, baseline data such as abdominal pain, bloating and dysfunctional defaecation were slightly higher in our study than in those reported by others studying a European population [21]. Higher VAS-IBS values may be explained by the fact that our patient population was actively seeking medical help in a university hospital perceived to be a centre of excellence.

The use of SB as a supplement to the standard drug therapy seemed to reflect the expectations of patients, especially those referred to a university hospital clinic. Patients often have their preferred drug regimen which may have evolved over time. They look for improvement of their current treatment than risk deterioration of symptoms by altering their drugs. Thus they are amenable to an addition to their medication. Interestingly, we observed that some patients perceived the study as a 'necessary choice' and, although they did not report satisfactory decrease of IBS symptoms, their attempts to discontinue the therapy often led to a rapid deterioration in their symptoms. This together with the characteristics of the patients actively seeking specialist care could potentially lead to under-reporting of symptom improvement in our report.

The absence of side effects indicates that the treatment is safe and well tolerated as a supplemental treatment. This is in concordance with previous studies indicating very low levels of SB toxicity [18]. The most commonly reported complaint following SB treatment is the unpleasant smell and taste but these are eliminated in the microencapsular formulation.

The results of the study suggest that MSB may be a useful supplement to standard IBS therapy. It significantly decreases the frequency of clinical symptoms including spontaneous abdominal pain, postprandial abdominal pain, abdominal pain during defaecation, stool consistency and constipation.

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