

TREATMENT OF POSTINFECTIOUS IRRITABLE BOWEL SYNDROME AND NONINFECTIVE IRRITABLE BOWEL SYNDROME WITH MESALAZINE

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ABSTRACT - Context - Recent studies support the hypothesis that postinfectious irritable bowel syndrome and some irritable bowel syndrome patients display persistent signs of minor mucosal inflammation. Mesalazine has intestinal anti-inflammatory properties including cyclooxygenase and prostaglandin inhibition. The effects of mesalazine on postinfectious irritable bowel syndrome and noninfective irritable bowel syndrome patients are still unknown. **Objective** - To observe the effects of mesalazine on postinfectious irritable bowel syndrome and noninfective irritable bowel syndrome with diarrhea patients. **Methods** - Based on Rome III criteria, 61 irritable bowel syndrome with diarrhea patients (18 years old or more) were included in the evaluation. Patients were divided into two groups: postinfectious irritable bowel syndrome group, with 18 patients medicated with mesalazine 800 mg 3 times a day for 30 days; noninfective irritable bowel syndrome group, with 43 patients medicated with mesalazine 800 mg 3 times a day for 30 days. Symptom evaluations at baseline and after treatment were performed by means of a four-point Likert scale including stool frequency, stool form and consistency (Bristol Stool Scale), abdominal pain and distension (maximum score: 16; minimum score: 4). **Results** - Postinfectious irritable bowel syndrome group presented a statistically significant reduction of the total symptom score ($P < 0.0001$). The stool frequency was significantly reduced ($P < 0.0001$), and stool consistency, improved ($P < 0.0001$). Abdominal pain ($P < 0.0001$) and abdominal distension were significantly reduced ($P < 0.0001$). Noninfective irritable bowel syndrome group presented a statistically significant reduction of total symptom score ($P < 0.0001$). Also, the stool frequency was significantly reduced ($P < 0.0001$) and stool consistency, improved ($P < 0.0001$). Abdominal pain ($P < 0.0001$) and abdominal distension were significantly reduced ($P < 0.0001$). There was no statistical difference between postinfectious irritable bowel syndrome group and noninfective irritable bowel syndrome group on total symptom score results at 30th day of therapy with mesalazine 800 mg 3 times a day. ($P = 0.13$). **Conclusion** - Mesalazine reduced key symptoms of postinfectious irritable bowel syndrome and noninfective irritable bowel syndrome with diarrhea patients.

HEADINGS – Inflammatory bowel diseases. Irritable bowel syndrome. Mesalamine.

INTRODUCTION

Acute infectious gastroenteritis is the strongest known risk factor for the development of irritable bowel syndrome (IBS)⁽³⁾. Six percent to 17% of unselected IBS patients believe their symptoms began with an infection, which is supported by prospective studies that show an incidence of postinfectious irritable bowel syndrome (PI-IBS) of 4% to 31% following bacterial gastroenteritis⁽²⁵⁾.

A number of risk factors have been associated with the development of PI-IBS, including the virulence of the pathogen, younger age, female sex, the long duration of the initial illness and the presence of psychological disturbances⁽³⁾. PI-IBS has been reported after *Campylobacter*, *Salmonella*, and *Shigella* infections.

Serial biopsies after *Campylobacter jejuni* gastroenteritis show an initial inflammatory infiltrate, with an increase in enterochromaffin cells (EC), which in most cases subsides over the next 6 months⁽²⁵⁾.

Patients who develop IBS show increased numbers of EC, and lymphocyte cell counts at 3 months compared to those who do not develop IBS^(18, 25). Individuals with PI-IBS are a clinically distinct subgroup characterized by diarrheal symptoms, less psychiatric illness, and increased serotonin-containing EC compared to those with non-PI-IBS⁽⁸⁾.

The increase in EC concentrations associated with PI-IBS may contribute to gastrointestinal symptoms through serotonin-mediated mechanisms^(1, 6). As EC are the primary source of intestinal serotonin — a

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neurotransmitter that stimulates enterocyte secretions and peristalsis — it is conceivable that increased cell numbers could lead to increased serotonin levels and subsequent diarrheal symptoms⁽²³⁾. Indeed, patients with PI-IBS have shown elevated postprandial plasma levels of serotonin compared to patients with IBS with constipation (IBS-C) or healthy volunteers^(9, 13, 22).

Recent studies support the hypothesis that Th2 cytokines induce muscle hypercontractility during infection by a direct action on smooth muscle. The maintenance of hypercontractility results from Th2 cytokine-induced expression of transforming growth factor (TGF-beta1) and the subsequent upregulation of cyclooxygenase 2 (COX-2) and prostaglandin E₂ (PGE-2) at the level of the smooth muscle⁽¹⁾. The same studies also support that COX-2 inhibitors attenuated TGF-beta1-induced muscle hypercontractility⁽¹⁾.

Mesalazine has intestinal anti-inflammatory properties including COX and prostaglandin (PG) inhibition. The effects of mesalazine on PI-IBS and noninfective IBS patients are still unknown and, to the best of our knowledge, the present study is the first to address the effect of mesalazine on PI-IBS.

METHODS

Based on Rome III (Figure 1) criteria, 61 IBS patients with diarrhea (IBS-D) (Figure 2), 18 years old or more, were included (Table 1). To exclude organic diseases, all patients underwent colonoscopy, stool culture, serum anti-endomysium antibody, lactose tolerance test and ova and parasite exam. Patients were divided into two groups: PI-IBS group (PIG), with 18 patients medicated with mesalazine 800 mg 3 times a day for 30 days; non-infective IBS group (NIG), with 43 patients medicated with mesalazine 800 mg 3 times a day for 30 days. Drugs that might have any effect on intestinal

motility or secretion were not allowed. Symptom evaluations at baseline and after treatment were performed by means of a 4. Likert scale (Figure 3), including stool frequency, stool form and consistency (Bristol Stool Scale), abdominal pain and distension (maximum score: 16; minimum score: 4). Paired *t* tests were used for statistical analyses.

This study was approved by the Ethics Committee in Human and Animal Research of Hospital Geral de Goiânia – CEPHA,

TABLE 1. Patients' demographic data and patients score at baseline

Groups/patients	NIG	PIG
Age (mean)	46	42
Males	13	7
Females	30	11
Stool frequency score (mean)	2.79	2.44
Stool form and consistency score (mean)	3.19	3.28
Abdominal pain score (mean)	2.58	2.22
Abdominal distension score (mean)	2.26	2.33
Total	43	18

NIG – non-infective IBS group

PIG – PI-IBS group

	1	2	3	4
1. Stool frequency	≤2	3	4 to 5	>5
2. Stool form and consistency	≤4	5	6	7
3. Abdominal pain	Absent	Mild	Moderate	Severe
4. Abdominal distension	Absent	Mild	Moderate	Severe

FIGURE 3. The symptom score evaluation submitted to all of the two groups of evaluated patients before and after 30 days of therapy (minimum score: 4; maximum score: 16)

Recurrent abdominal pain or discomfort* at least 3 days/month in the last 3 months associated with two or more of the following:

1. improvement with defecation
2. onset associated with a change in frequency of stool
3. onset associated with a change in form (appearance) of stool

In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 days a week during screening evaluation is recommended for subject eligibility

* "discomfort" means an uncomfortable sensation not described as pain

** criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

FIGURE 1. Diagnostic criterion** for irritable bowel syndrome

In order to subtype patients according to bowel habit for research or clinical trials, the following subclassifications may be used (Bristol Stool Form Scale). The validity and stability of such subtypes over time is unknown and should be subjects of future research.

1. IBS-C: hard or lumpy stools^a at least 25% and loose (mushy) or watery stools^b <25% of bowel movements*
2. IBS-D: loose (mushy) or watery stools^b at least 25% and hard or lumpy stool^a <25% of bowel movements*
3. IBS-M: hard or lumpy stools^a at least 25% and loose (mushy) or watery stools^b at least 25% of bowel movements*
4. Unsubtyped IBS: insufficient abnormality of stool consistency to meet criteria for IBS-C, D, or M*

* In the absence of antidiarrheal or laxative use

IBS-C: irritable bowel syndrome with constipation;

IBS-D: irritable bowel syndrome with diarrhea;

IBS-M: mixed irritable bowel syndrome

FIGURE 2. Subtyping irritable bowel syndrome by predominant stool pattern

Goiânia, GO, Brazil, in August, 12, 2008 (Protocol CEPHA – HGG 381/08) and was conducted at offices and at Research Center of Instituto Goiano de Gastroenterologia. All patients answered previously to an Informed Consent. The period of time for data collection was from August/2008 to December/2008.

RESULTS

NIG presented a statistically significant reduction ($P < 0.0001$) of the total symptom score (Figure 4). Also, the stool frequency (Table 2) was significantly reduced ($P < 0.0001$) and the stool consistency, improved ($P < 0.0001$). The abdominal pain ($P < 0.0001$) and abdominal distention were significantly reduced ($P < 0.0001$). PIG presented a statistically significant reduction ($P < 0.0001$) of the total symptom (Figure 5). The stool frequency (Table 3) was significantly reduced ($P < 0.0001$) and the stool consistency, improved ($P < 0.0001$). Abdominal pain ($P < 0.0001$) and abdominal distention were significantly reduced ($P < 0.0001$).

Groups PIG and NIG showed no significant statistical difference on total symptom score at 30th day after mesalazine treatment (Figure 6).

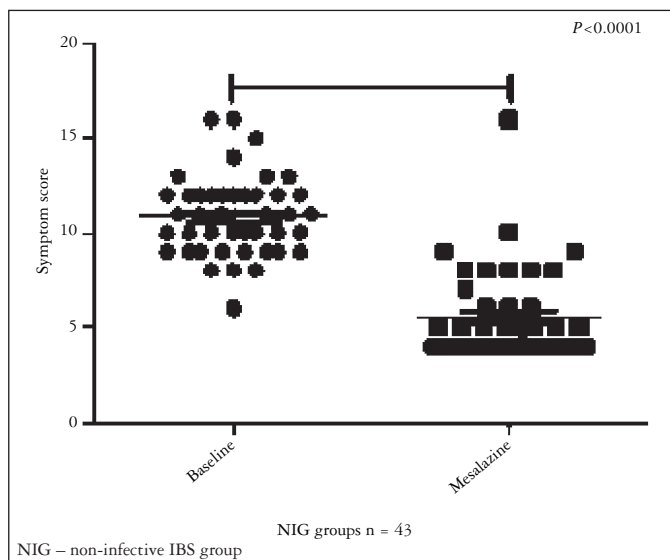


FIGURE 4. NIG total symptom score at baseline and at 30th day therapy with mesalazine 800 mg 3 times a day

TABLE 2. NIG patients score of symptoms before and at 30th day with mesalazine 800 mg 3 times a day

Symptoms	Before	30th day
Stool frequency score – mean (SD)	2.79 (0.67)	1.44 (0.70)*
Stool form and consistency score – mean (SD)	3.19 (0.55)	1.60 (0.82)*
Abdominal pain score – mean (SD)	2.58 (0.82)	1.35 (0.61)*
Abdominal distension score – mean (SD)	2.26 (0.88)	1.66 (0.64)*
Total	43	43

* $P < 0.0001$

NIG – non-infective IBS group
SD = standard deviation

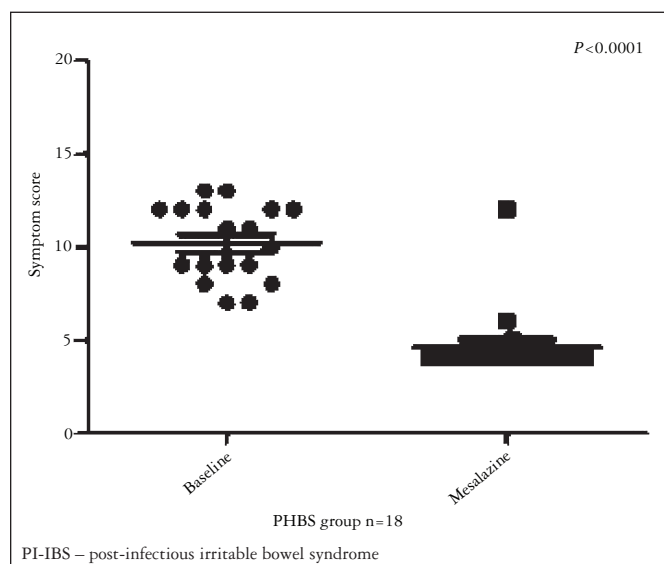


FIGURE 5. PI-IBS group total symptom score at baseline and at 30th day therapy with mesalazine 800 mg 3 times a day.

TABLE 3. PIG patients score of symptoms before and at 30th day with mesalazine 800 mg 3 times a day

Symptoms	Before	30th day
Stool frequency score – mean (SD)	2.44 (0.62)	1.11 (0.47)*
Stool form and consistency score – mean (SD)	3.28 (0.57)	1.11 (0.47)*
Abdominal pain score – mean (SD)	2.22 (0.73)	1.17 (0.51)*
Abdominal distension score – mean (SD)	2.33 (0.84)	1.11 (0.32)*
Total	18	18

* $P < 0.0001$

PIG – PI-IBS group
SD = standard deviation.

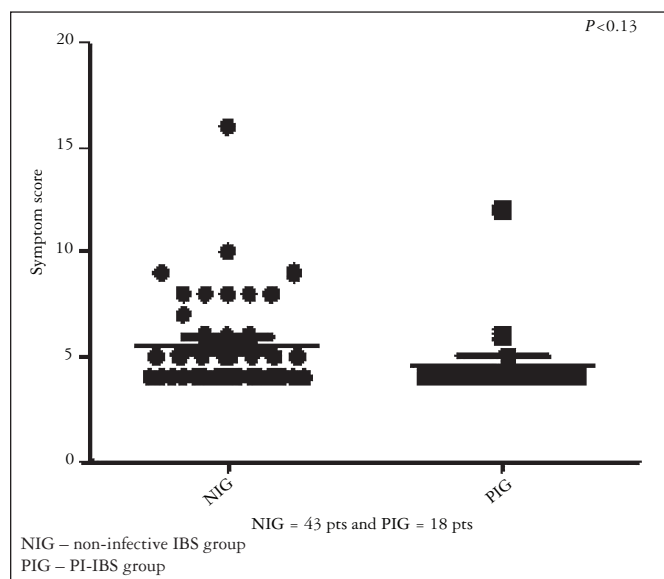


FIGURE 6. Results of NIG and PIG total symptom score at 30th day therapy with mesalazine 800 mg 3 times a day

DISCUSSION

A unifying hypothesis to explain the pathogenesis of IBS remains elusive. Alterations in gastrointestinal motor function, enhanced visceral perception of painful stimuli and psychosocial factors are considered key contributors to symptom generation in IBS^(2, 7, 12, 14, 24). Recently, recognized factors include reduced ability to expel intestinal gas, altered central processing of afferent signals and intestinal inflammation.

While routine histological examination reveals no significant colonic mucosal abnormality on the majority of these patients, recent quantitative histological, immunohistochemical and ultrastructural analyses provide evidence of subtle morphologic changes in these patients⁽²⁾.

There are numerous studies indicating that mucosal biopsies in both PI-IBS and IBS-D show increased numbers of CD3⁺ lymphocytes^(5, 8). Different researchers have looked at different classes of immunocytes, but there is a broad agreement on the increase in CD3⁺ lymphocytes; also, increases in CD25⁺ lymphocytes were shown, indicating the presence interleukin-2 receptor, a marker of activated lymphocytes⁽⁵⁾. Patients who developed PI-IBS had higher interleukin 1B concentrations compared to those who had not had an acute episode of diarrhea⁽¹³⁾.

In addition to increased concentrations of inflammatory mediators and cells, increased small bowel permeability may also be involved in pathogenesis of PI-IBS. Intestinal permeability, determined by the ratio of lactulose to manitol excreted in urine, was significantly higher in PI-IBS patients compared to controls⁽²²⁾. Several authors have suggested that increased intestinal permeability may allow the access of bacterial and luminal antigens to the submucosa, which could perpetuate chronic inflammation and disrupt enteric sensation and motility, that have been implicated in the pathogenesis of IBS^(7, 14, 17, 24).

Recent studies support the hypothesis that Th2 cytokines induce muscle hypercontractility during infection by a direct action on smooth muscle. The maintenance of hypercontractility results from Th2 cytokine-induced expression of the transforming

growth factor (TGF-beta 1) and the subsequent upregulation of COX-2 and PGE-2 at the level of the smooth muscle⁽¹⁾. The same studies also support that COX-2 inhibitors attenuated TGF-beta 1-induced muscle hypercontractility⁽¹⁾.

Mesalazine is known to have anti-inflammatory properties and is used in the treatment of inflammatory bowel diseases. Although its exact mechanism are still unknown^(10, 20), several potential mechanisms have been suggested, including 5-aminosalicylate-induced inhibition of inflammation by interfering with the metabolism of arachidonic acid, prevention of mucosal generation of leukotrienes and PG⁽²⁶⁾ scavenging of free radicals^(21, 26) and mechanisms only recently identified involving inhibition of nuclear factor-kappaB (NFκB) and induction of apoptosis^(4, 15, 19, 27, 28).

Further properties include changes in the production of immune globulins and diminished production of interleukin-1, as well as partial inhibition of platelet activating factor (PAF) expression, resulting in a decrease in leucocyte trafficking⁽¹⁶⁾. Moreover there are evidences that mesalazine has a potential inhibition on mast cell histamine release⁽¹¹⁾.

In this study, mesalazine, compared to baseline, presented clinical improvement of stool frequency, stool form and consistency (Bristol Stool Scale), abdominal pain and abdominal distension in PI-IBS and non-infective IBS-D patients. There was no statistical difference when comparing the results of total symptom score of PI-IBS and noninfective IBS-D patients.

The limitations of this study was the small number of IBS-PI patients (18) compared to non-infective IBS-D (43), and the follow-up period of 30 days using mesalazine, that might increase the possibility of placebo effect.

Even considering these limitations, we observed good clinical results with mesalazine, an anti-inflammatory drug, in PI-IBS and non-infective IBS-D, supporting previous studies that suggest a low grade bowel inflammation in these groups of patients.

In conclusion, mesalazine reduced key symptoms of PI-IBS and noninfective IBS-D patients. These preliminary results warrant further larger placebo-controlled studies.

Bafutto M, Almeida JR, Leite NV, Oliveira EC, Gabriel-Neto S, Rezende-Filho J. Tratamento da síndrome do intestino irritável pós-infecciosa e da síndrome do intestino irritável não-infecciosa com mesalazina. *Arq Gastroenterol.* 2011;48(1):36-40.

RESUMO - Contexto - Estudos recentes sustentam a hipótese que a síndrome do intestino irritável pós-infecciosa e alguns pacientes com síndrome do intestino irritável mostram sinais menores de inflamação persistente da mucosa. A mesalazina tem propriedades anti-inflamatórias intestinais, incluindo a inibição da ciclooxigenase e das prostaglandinas. Os efeitos da mesalazina na síndrome do intestino irritável pós-infecciosa e em pacientes com síndrome do intestino irritável não-infecciosa ainda são desconhecidos. **Objetivo** - Observar os efeitos da mesalazina em pacientes com síndrome do intestino irritável pós-infecciosa e síndrome do intestino irritável com diarreia não-infecciosa. **Métodos** - Com base nos critérios de Roma III, 61 pacientes síndrome do intestino irritável acompanhado de diarreia (18 anos ou mais de idade) foram incluídos na avaliação. Os pacientes foram divididos em dois grupos: grupo síndrome do intestino irritável pós-infecciosa, com 18 pacientes medicados com mesalazina 800 mg 3 vezes ao dia por 30 dias; grupo síndrome do intestino irritável não-infecciosa, com 43 pacientes medicados com mesalazina 800 mg 3 vezes ao dia por 30 dias. Avaliações dos sintomas no início e após o tratamento foram realizadas por meio de uma escala Likert de 4 pontos, incluindo a frequência das evacuações, forma e consistência das fezes (Bristol Stool Scale), dor e distensão abdominal (pontuação máxima: 16; pontuação mínima: 4). **Resultados** - O grupo síndrome do intestino irritável pós-infecciosa apresentou redução estatisticamente significativa do escore total de sintomas ($P < 0,0001$). A frequência de evacuações foi significativamente reduzida ($P < 0,0001$) e a consistência das fezes melhoraram ($P < 0,0001$). Dor abdominal ($P < 0,0001$) e distensão abdominal foram significativamente reduzidas ($P < 0,0001$). O grupo síndrome do intestino irritável não-infecciosa apresentou redução estatisticamente significativa do escore total de sintomas ($P < 0,0001$). Além disso, a frequência de fezes foi significativamente reduzida ($P < 0,0001$) e a consistência das fezes melhoraram ($P < 0,0001$). Dor abdominal ($P < 0,0001$) e distensão abdominal foram significativamente reduzidas ($P < 0,0001$). Não houve diferença estatística entre o grupo síndrome do intestino irritável pós-infecciosa e o grupo síndrome do intestino irritável não-infecciosa sobre os resultados da pontuação total dos sintomas em 30 dias de terapia com mesalazina 800 mg 3 vezes ao dia ($P = 0,13$). **Conclusão** - O uso de mesalazina reduziu os principais sintomas da síndrome do intestino irritável pós-infecciosa e da síndrome do intestino irritável com diarreia não-infecciosa.

DESCRITORES - Enteropatias inflamatórias. Síndrome do intestino irritável. Mesalazina.

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