

Clinical, endoscopical and morphological efficacy of mesalazine in patients with irritable bowel syndrome

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Objectives: The aim of this study was to analyze the clinical efficacy and cytomorphologic changes of colon mucosa following the treatment of patients suffering from irritable bowel syndrome (IBS) with mesalazine (5-aminosalicylic acid [5-ASA]).

Methods: In this controlled, randomized, blind clinical trial, a total of 360 patients with varying subtypes of IBS were randomly treated with 500 mg of mesalazine qid or by standard therapy without mesalazine for a period of 28 days. Pre- and post-treatment pain intensity, pain duration, meteorism, stool abnormalities and endoscopic parameters were monitored, and biopsies or brush biopsies were examined histologically.

Results: Treatment of IBS patients with mesalazine significantly reduced intensity and duration of pain in all subtypes of IBS, except for duration of pain in the subtype “undifferentiated”, where the difference was not significant. In addition, in patients with diarrhea type and undifferentiated type of IBS, mesalazine also significantly reduced the abnormal stool pattern. In comparison to the control group, administration of mesalazine reduced the incidence of endoscopic and cytomorphologic changes of the bowel mucosa, including changes in colon mucus, mucus production, cytologic or histologic parameters, epithelial cell degeneration, appearance of leukocytes and macrophages and cell infiltrations.

Conclusion: Mesalazine was effective in reducing several symptoms characteristic of IBS. It significantly reduced pain intensity and duration and improved cytohistologic parameters of the bowel mucosa.

Keywords: 5-amino salicylic acid, 5-ASA, abdominal pain, irritable bowel syndrome, IBS, meteorism, stool abnormalities

Introduction

Irritable bowel syndrome (IBS) is the most common functional bowel disorder. It is characterized by abdominal pain, bloating and disturbed defecation. The first report on IBS dates to 1818.¹

Morbidity varies from 30% to 50% in Europe, the United States and Japan, and amounts to more than 60% in post-Soviet countries.²⁻⁴ In spite of numerous attempts to discover the triggers, etiology and pathogenesis, the pathophysiology of the disease is still unclear. The influence of psychogenic disorders, visceral hypersensitivity and abnormal bowel motility in genesis of IBS is broadly acknowledged.^{3,5,6}

Bowel infections, bacterial overgrowth syndrome, antibiotics, stress and unfavorable dietary habits can precede visceral hypersensitivity and lead to a clinical manifestation of IBS. Although there is no specific morphologic correlate of IBS,

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these predictors can affect the colon microbiota and the local immune system, decrease the protective properties of the bowel mucosa, impair mucus production, and may be caused by only minimal alterations on the cellular level.

Histomorphologic analysis of biopsies in IBS is often negative with respect to pathological findings. Occasionally minimal violations or initial signs of edema of the colon mucosa, an increase in diameter of capillaries, constriction or dilatation of crypts, abundance of mucus in crypts, slight increase in number of goblet cells, dystrophy of solitary epithelial cells, increased number of fibroblasts within the stroma and cellular infiltrations are detectable. The detection of minor lesions is often accompanied by a decrease of proliferation and enhanced apoptosis of colonocytes.^{3,7} Progression of the disease leads to more pronounced morphological changes of the colon mucosa epithelium: reduced frequency of serotonin-producing cells and mast cells and increased frequency of secondary cells and increasing number of cellular infiltrations by eosinophils, neutrophils, lymphocytes, plasmocytes and fibroblasts of stroma.⁷ These morphological criteria are signs of inflammatory processes and activation of immune mechanisms, and could explain why IBS often is refractory to standard types of treatment. Elimination of inflammatory processes in colon mucosa could be one of the most promising targets of therapy for IBS patients.

Progress in the development of diagnostic tools, such as positron emission tomography and functional magnetic resonance imaging of the brain, have contributed considerably to understanding of the brain-gut interaction,^{8,9} indicating a possible psychophysiologic component,^{10,11} in addition to the hypothesis that altered motility is the primary underlying pathophysiologic basis of IBS. Most recently, evidence has accumulated suggesting that immune activation affects intestinal function and sensory perception as part of symptom generation in patients with IBS.^{12,13} However, these results are controversial, because contradictory results have been presented by several authors.^{14,15}

The first attempt to classify IBS was published by Manning et al¹⁶ followed by Kruis et al six years later.¹⁷ Several consensus conferences subsequently tried to develop diagnostic criteria for the classification and safe diagnosis of gastrointestinal disorders ("Rome criteria"^{18–20} Table 1, Table 2). The validity of the Rome criteria has been reported in several studies.^{21,22}

Due to the uncertainty of the pathophysiologic basis of IBS, numerous studies attempted to find a rationale for

Table 1 Diagnostic criteria according to the latest issue of "Rome III"²

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

Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Notes: *"Discomfort" means an uncomfortable sensation not described as pain. 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.

the reliable pharmacological treatment of this disease. The failure of corticosteroids stimulated the targeting of the immune system, eg, by mast cell stabilizers.¹⁴ Moreover, the therapeutic potential of aminosalicylates, well known for their benefits in chronic inflammatory bowel diseases, has attracted renewed interest as a potential cure for IBS.¹² To better study both relief and outcome in IBS, the Rome foundation initiated a complex systematic review and meta-analysis of the psychometric and performance characteristics of primary endpoints used in large multicenter therapeutic trials for irritable bowel syndrome using pharmacological approaches.²³

Patients and methods

Study sites and design

The study was performed in three centers in the Ukraine between 2006 and 2009, as a controlled post-marketing observational study with 360 patients diagnosed with an irritable bowel syndrome and sub-grouped in accordance with the Rome III criteria.

As a primary outcome parameter, we selected pain intensity. Secondary parameters were pain duration, meteorism, stool abnormalities and histocytologic parameters.

Table 2 Subtyping of IBS by predominant stool pattern modified according to Longstreth²

1. IBS with constipation (IBS-C) – hard or lumpy stools^a $\geq 25\%$ and loose (mushy) or watery stools^b $< 25\%$ of bowel movements^c.
2. IBS with diarrhea (IBS-D) – loose (mushy) or watery stools^b $\geq 25\%$ and hard or lumpy stool^a $< 25\%$ of bowel movements^c.
3. Mixed IBS (IBS-M) – hard or lumpy stools^a $\geq 25\%$ and loose (mushy) or watery stools^b $\geq 25\%$ of bowel movements^c.
4. Undifferentiated (IBS-U) – insufficient abnormality of stool consistency to meet criteria for IBS-C, -D, or -M^c.

Notes: ^aBristol Stool Form Scale 1–2 (separate hard lumps like nuts [difficult to pass] or sausage-shaped but lumpy); ^bBristol Stool Form Scale 6–7 (fluffy pieces with ragged edges, a mushy stool or watery, no solid pieces, entirely liquid); ^cIn the absence of use of antidiarrheals or laxatives.

Ethics

The study was approved by the ethics committees of the National Medical University of Donetsk and the Gastroenterological Center of Poltava Hospital Clinic, Poltava, Ukraine, according to the legal requirements of the State of Ukraine.

Diagnosis of IBS

Diagnosis of IBS was established according to Rome III criteria (2006) and included: Recurrent abdominal pain or discomfort for ≥ 3 days per month during the last 3 months, associated with ≥ 2 of the following:

- Improvement of defecation
- Changes in stool frequency
- Changes in stool consistency

Diagnostic criteria needed to have been fulfilled for the last 3 months with symptom onset ≥ 6 months prior to diagnosis.

Patients with IBS were divided into subgroups depending on stool pattern according to the Bristol Stool Form Scale.

Occurrences of infections were assessed by anamnesis from the beginning throughout the duration of IBS. Post infectious IBS was considered as a special form of IBS: we did not exclude this group of patients from the study. Absence of any bowel infection was confirmed by microbiological stool examination before diagnosis of IBS and inclusion into the study.

Any organic pathology was excluded first of all (in compliance with Rome III criteria) by exclusion of the specific alarm symptoms such as first symptoms at age ≥ 50 years, loss of weight, blood in stool, fever, cancer anamnesis in relatives.

Besides histomorphologic analysis of the biopsies we proved absence of any organic pathology or infection. Evidence of inflammation (hyperemia, edema, granulations) were considered as a mild inflammatory process in IBS.

Genetic predisposition to IBS was not found in investigated patients. Different dietary abnormalities associated with specific IBS types (constipation or diarrhea) were found in all patients. However, patients with a strict diet regimen (eg, vegetarians) were excluded from the study.

Statistical analysis

Statistical analysis started from verification of results of normal dispensation by W-test (Shapiro–Wilk) and Chi-square test. Descriptive statistics with calculation of mean values, standard deviations and median were

performed. Significance of differences of mean values was determined by Student's *t*-test.

Patients

A total of 240 patients from an industrial region with unfavorable ecology and 120 patients from an agricultural region without this negative impact were recruited. The gender distribution was 105 (29.2%) men and 255 (70.8%) women. Average age was 43.2 ± 3.3 years. Diagnosis of IBS and sub-grouping was based on clinical symptoms according to Rome III criteria, 2006,² as described in Table 2.

Patients were randomized in 2 groups. Each third patient with any type of IBS was assigned to the treatment group and obtained mesalazine (Salofalk®) 2.0 g per day for 28 days. Thus 120 IBS patients received 500 mg tablets qid after a meal. The remaining 240 IBS patients were assigned to the control group and received a standard treatment without mesalazine.

Standard treatment according to Rome III was followed during the investigation. Patients with diarrhea received loperamide (2–4 mg when necessary), patients with constipation received psyllium husks (Plantago ovata, Mucofalk®, 3.25 g bid with meals) or lactulose syrup (15–20 mL bid); patients with abdominal pain syndrome received mebeverine 400 mg per day. Some patients with severe meteorism received simethicon limited to 3–5 days.

Before and after treatment, patients characterized their pain intensity by a visual-analog scale (0 = no pain to 10 = worst imaginable pain). Duration of pain, incidence of meteorism and stool abnormalities were queried and documented by the physicians.

Endoscopy was done for all patients before and after treatment. Colonoscopy was done for 200 patients and sigmoidoscopy for 160 patients. During endoscopy the color and intensity of hyperemia, evidence of edema and granulations scattering reflected light in colon mucosa were investigated. Characteristics of vascular pattern, presence of mucus on the colon wall and haustrations were also analyzed.

Before and after 1 month of treatment, endoscopy was carried out on each patient by the same physician.

In addition to visual examination during endoscopy, biopsies of the colon mucosa were taken in 90 patients, but in 150 patients brush-biopsies were preferred.

Brush-biopsies were performed by an abrasive brush brought in contact with visually abnormal or suspicious areas of the colon mucosa. Thereafter the material was transferred to a microscope slide and air dried. The samples were then stained according to the Pappenheim method

(May-Grünwald-Giemsa solution, ie, methylene blue plus eosin in a methanolic solution for 3 minutes). In brush-biopsies the number and type of epithelial cells, leukocytes, erythrocytes, lymphocytes and bacteria were analyzed.

For histologic analysis, biopsies of the colon mucosa were chemically fixed in a 5% formaline solution, subjected to a conventional paraffin embedding procedure and subsequent staining of the 2–3 μm sections by hematoxyline-eosin-alcian blue at pH 1.0 and 2.5 for the determination of sulfated and non-sulfated glucosaminoglycans and glycoproteins, and for goblet cells and colon mucus. To characterize the mucus production, the Periodic Acid Schiff reaction (PAS-reaction) was used.

Histological sections were examined with respect to the number and maturity of goblet cells as well as the amount and maturity of the mucus. Furthermore, the intensity of cell infiltrations and their character was determined.

Results

Patients' age and duration of IBS symptoms

A total of 291 (80.8%) patients came down with IBS before the age of 45 years. In 7.5% of all patients IBS was diagnosed between 56 and 65 years of age (no significant

difference between males and females). The incidence of IBS was highest in males at the age between 26 to 35 years ($n = 39$, 37.1% [$P < 0.01$ as compared with females, $n = 60$, 23.5% and as compared with the total, $n = 99$, 27.5%]). The highest incidence of IBS in women was in the age group of 15–25 years. There was no significant difference in the age distribution of women compared with the intention-to-treat population (Figure 1).

At first diagnosis, duration of IBS varied from 6 months to 25 years. Most females had symptoms of IBS for a period of 5–10 years (79.4% of this group, $n = 81$), most males suffered from IBS for a period of 1–3 years (35.9% of this group, $n = 42$) (Figure 2).

At first diagnosis, patients were allocated to four categories of IBS according to the Rome III criteria: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS mixed (IBS-M) and IBS undifferentiated (IBS-U) (Figure 3). Overall, IBS-C was the most frequent category (43.3% or 156 of 360), which was most infrequent in the age group of 36–45 (26.5%), followed by the IBS-D category (35.0% or 126 of 360). The IBS-D category predominated in age groups from 18–45 years, with lower incidence at an age above 46 years. The mixed type IBS-M was diagnosed in 57 patients

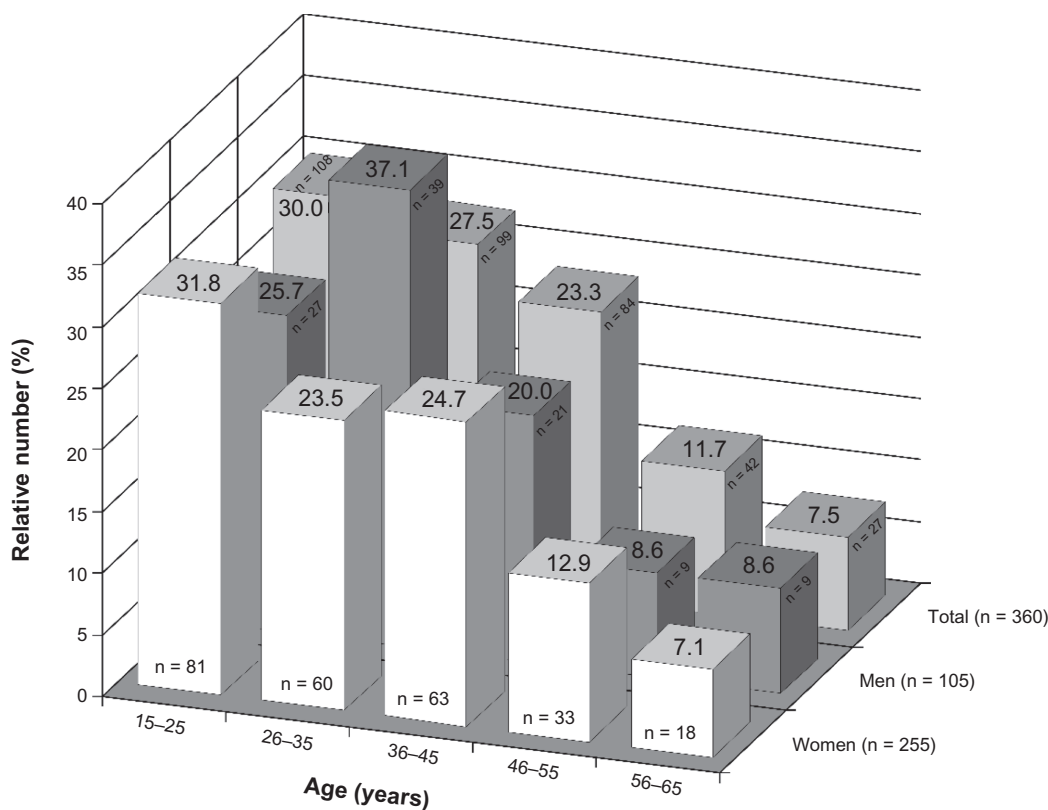


Figure 1 Gender-dependent age distribution of patients at onset of IBS symptoms.
Abbreviation: IBS, Irritable Bowel Syndrome.

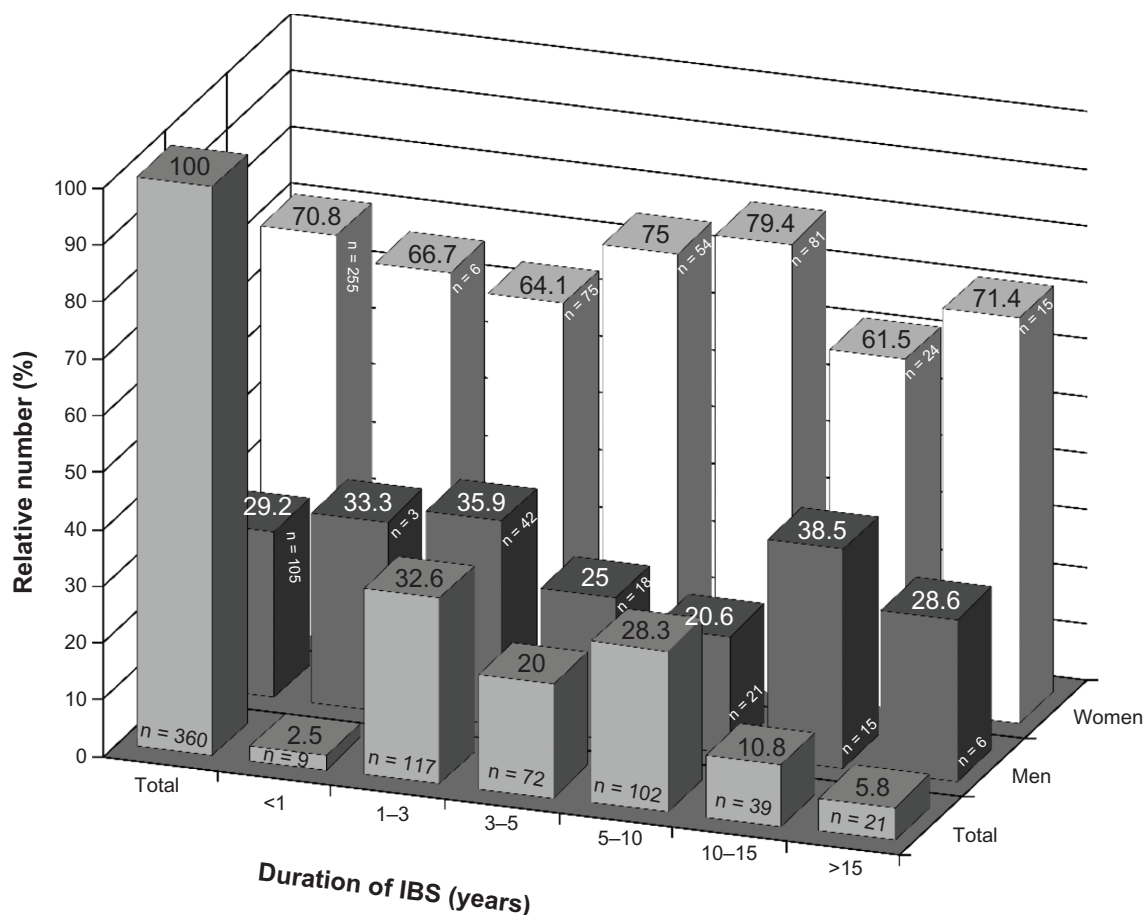


Figure 2 Gender-dependent distribution of duration of IBS symptoms at first diagnosis.
Abbreviation: IBS, Irritable Bowel Syndrome.

(15.8%) and prevailed in the two age groups 18–25 and 36–45 years. IBS-U was diagnosed in a total of 5.8% of patients, the percentage increasing with age of patients, ie, it was most frequently diagnosed in the older patients.

We also determined the incidence of predisposing factors for IBS. The factors occurring most frequently were stress (40.8%) and chronic urogenital disorders (35.6%) followed by bowel infections (27.5%), low physical activity (25.8%) and obesity (20.0%) (Figure 4).

Efficacy

Pain intensity

Intensity of pain before treatment and after 28 days' therapy with either mesalazine or conventional therapy without mesalazine was judged by the patients on a visual analog scale (0–10). In all IBS categories, the pain intensity was significantly lower in the mesalazine group (1.4 ± 0.4 , $n = 120$ of 360 patients) compared with the control group (3.8 ± 0.6 , $n = 240$ of 360 patients: see Figure 5). The highest pain score was determined in the IBS-U group (8.7 ± 0.9), which was

significantly higher compared to the other pain scores before treatment, except for the pain score in IBS-M. Mesalazine was less effective in IBS-M and IBS-U, albeit significantly better compared with controls within each particular IBS-category. The difference between the pain score in the mesalazine group with IBS-U is significant, compared with all other groups ($P < 0.01$).

Pain duration

Pain duration was queried and recorded by the physicians. The most unfavorable situation was found in the IBS-U group, where the mean pain duration was highest (11.0 ± 1.2 hours per day). This level of pain duration at baseline was significantly higher compared with all other baseline values. Moreover, in this group, there was no difference between the treatment with mesalazine and the control group. In all other IBS categories mesalazine treatment reduced pain duration significantly (Figure 6). The most pronounced reduction in pain duration occurred in the IBS-C and IBS-D group.

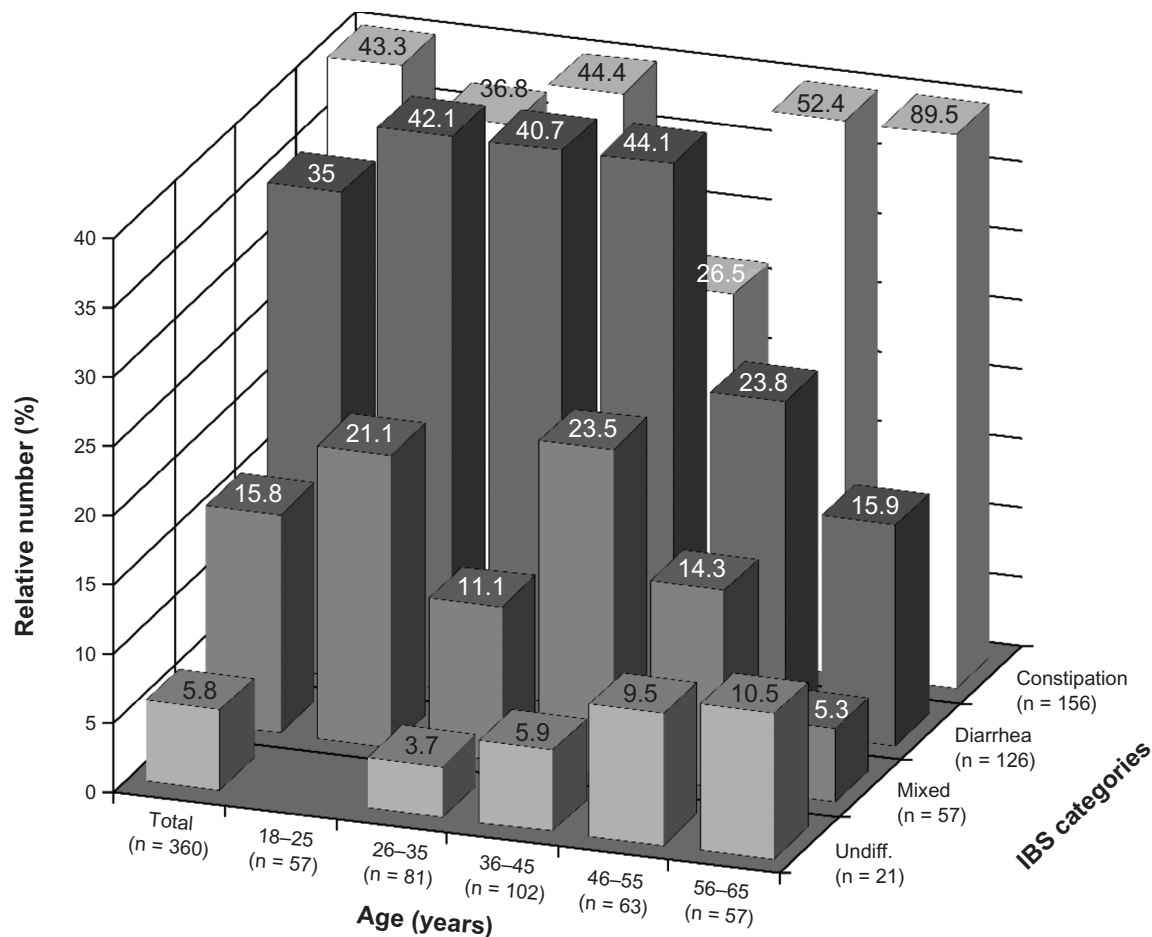


Figure 3 Age distribution of IBS categories.
Abbreviation: IBS, Irritable Bowel Syndrome.

Incidence of stool abnormalities

At baseline, stool abnormalities were present in all patients. By mesalazine treatment, the number of patients with stool abnormalities was significantly reduced in the IBS-D and IBS-U group only. In each case, the treatment of IBS by standard or mesalazine therapy provided a significant reduction in the percentage of patients with stool abnormalities (Figure 7).

Incidence of meteorism

At baseline most patients suffered from meteorism. Standard therapy and therapy including mesalazine reduced the number of patients with meteorism significantly in all IBS categories. The difference between standard therapy and mesalazine therapy was significant only in the IBS-D and the IBS-M group (Figure 8).

Cytomorphologic findings

Results of a cytomorphologic analysis of brush biopsies in patients with different categories of IBS at baseline, which

was performed to assess possible differences between IBS categories, are presented in Figure 9. Figure 9 includes only cytomorphologic parameters with significant differences to the basic population. Significant differences were seen between the basic population ($n = 150$) and the IBS-C group (significantly less “epithelial cells with degeneration”, column 3), the IBS-D group (significantly more “pavement cells without changes”, column 1, and significantly lower incidence of “mixed bacterial flora”, column 5), the IBS-M group (significantly more “columnar epithelial cells”, column 2), and the IBS-U group (significantly higher incidence of “nuclear polymorphism in epithelial cells”, column 4, and significantly higher incidence of “mixed bacterial flora”, column 5).

Incidence of cytomorphologic parameters following treatment with mesalazine compared with the control group considered the parameters “colon mucus changes”, “cytological or histological changes”, “epithelial cell degeneration”, “singular leukocytes or macrophages”, “mild cell infiltrations” and “mucus production” (Figure 10, pairs of columns 1–6).

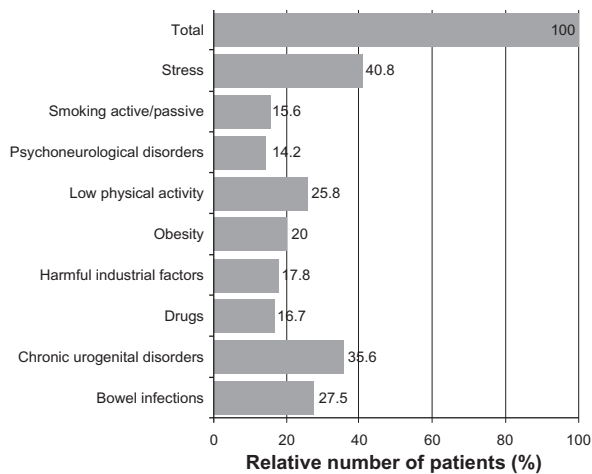


Figure 4 Frequency of predisposing factors (100% equals $n = 360$).

The parameters “epithelial cell degeneration” (column 3) and “mucus production” (column 6) showed no significant difference between mesalazine treatment and controls. With all other parameters the difference between treatment and controls was significant ($P < 0.05$, columns 1 and 4; $P < 0.01$, columns 2 and 5), ie, reduction of colon mucus changes, reduction of cytologic or histologic changes, reduction of singular leukocytes or macrophages and less cell infiltrations as a result of mesalazine treatment.

Cell infiltrations were found in 2 (6.7%) patients, who received mesalazine in contrast to 20 (33.3%) patients in the control group ($P < 0.01$). Abnormal mucus production was seen in 8 (26.7%) patients in the mesalazine group and 27 (45.0%) patients in the control group (Figure 10).

Most patients with cytomorphologic changes after treatment were between 38 and 47 years old, suffered from IBS for more than 3 years, and had several predisposing factors and endoscopic changes before treatment. 12 of 34 (35.3%) patients from this group suffered from constipation type IBS.

For morphological evaluation of peculiarities of the colon mucosa, histological analyses were performed in 90 IBS patients who had signs of inflammatory reactions during endoscopic examination. The histologic pattern and changes of the intensity of the colon mucosa showed considerable variations. Abnormal mucus production and moderate inflammatory changes prevailed in the IBS patients examined. A number of 39 (43.3%) patients had a regular columnar epithelium, single goblet cells and normal numbers of endocrinocytes (Figure 11).

A flattening of the superficial epithelium of 10–15 μm was found in 30 (33.3%) patients, and foci of desquamation in 18 (20.0%) IBS patients (Figure 12).

An abundance of crypts with a diameter of 80 μm was observed. Goblet cells in crypts predominated in 50 (55.6%) IBS patients at the mucus production phase, which could be evidence of mucus hyperproduction (Figure 13). In 41 (45.6%) patients, the structure of goblet cells appeared normal. The composition of mucus had changed in 52 (57.8%) IBS patients. In 32 (35.6%) patients, the balance between sulfated and non-sulfated glucosaminoglycans and glycoproteins was altered according to the alcian blue staining (data not shown). The level of sulfated glycoproteins had increased. In 20 (22.2%) IBS patients a minor decrease in PAS-reaction of mucus in goblet cells was observed (data not shown).

Edemata of the intercryptal space were present in 35 (38.9%) patients (Figure 14B). At all investigated biopsies mild cell infiltrations could be seen. The infiltrates consisted of plasmocytes (40%–50%) and lymphocytes (30%–40%); evidence of eosinophils and fibroblasts was found in the basal part of the mucosa (37 patients, 41.1%; Figure 14A, B).

In the submucous layer abnormal vascular patterns were present in 64 (71.1%) IBS patients. Abundant venous microcapillaries and sometimes venous stasis phenomena were present. Occasionally, foci of lymphoid and plasmocytic infiltrations and lymphoid follicles were detected in the submucosal layer (Figure 15A, B).

Safety analysis

The frequency of adverse events (AEs), clinically relevant changes in laboratory analysis and vital signs were assessed. A total of 44 AEs were reported in 42 (11.7%) patients. Among them 13 patients (10.8%) obtained mesalazine and standard treatment and 29 patients (12.1%) received standard treatment only. No drug-related AEs were revealed in either group. The AEs most frequently reported in both groups of patients were headache, nasopharyngitis, and flu-like infection. There was no significant difference in frequency of these AEs in the two groups. All patients who reported AEs, experienced AEs of mild intensity. There was no evidence for serious AEs in IBS patients during the study.

Discussion

The pathophysiology of IBS has long been discussed and is still to be elucidated. The Rome Foundation has spent many years collecting data from experts and updating our knowledge about this disease,^{2,23} a process that continuously results in improvement in diagnosis and characterization of different aspects of IBS and thus the optimization of individual patient-oriented therapies.

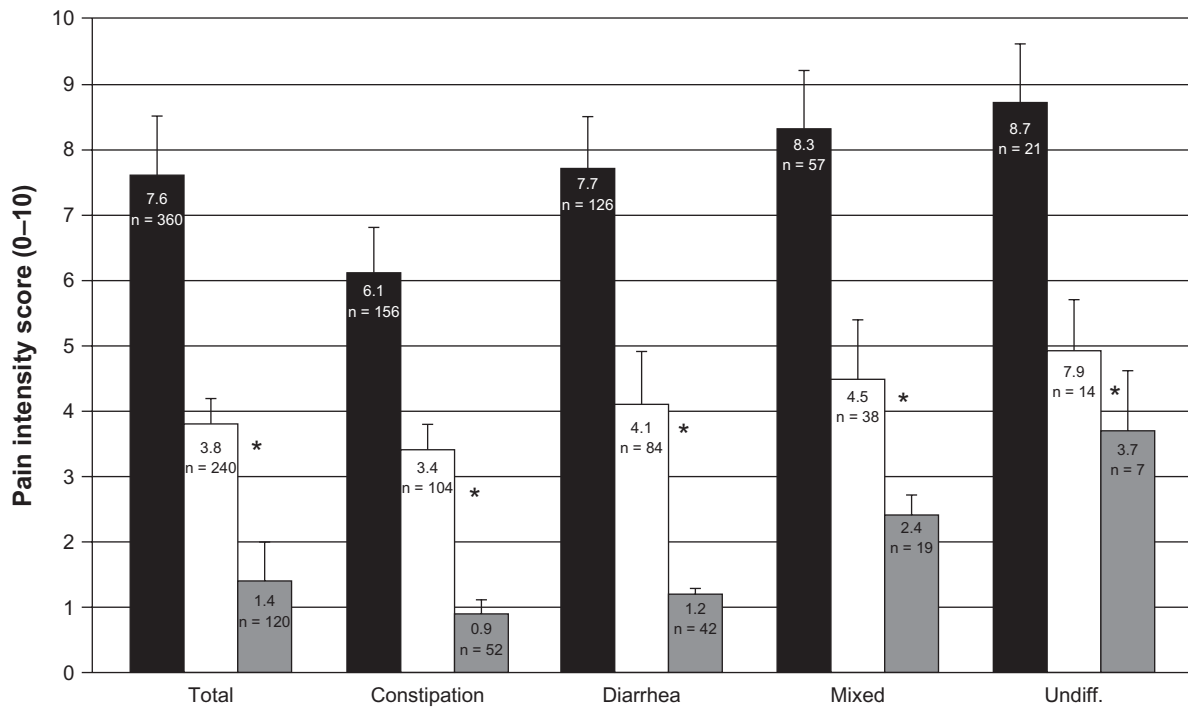


Figure 5 Pain intensity judged by patients with different categories of IBS (constipation, diarrhea, mixed and undifferentiated type) on a visual analog scale (0–10). **Notes:** “Total” refers to the intention to treat population; columns with significant difference between control and mesalazine group are marked by * ($P < 0.05$). Values before treatment are represented by black columns, control group values are in white columns and values from the mesalazine group are in gray. Vertical bars represent standard deviations.

Abbreviation: IBS, Irritable Bowel Syndrome.

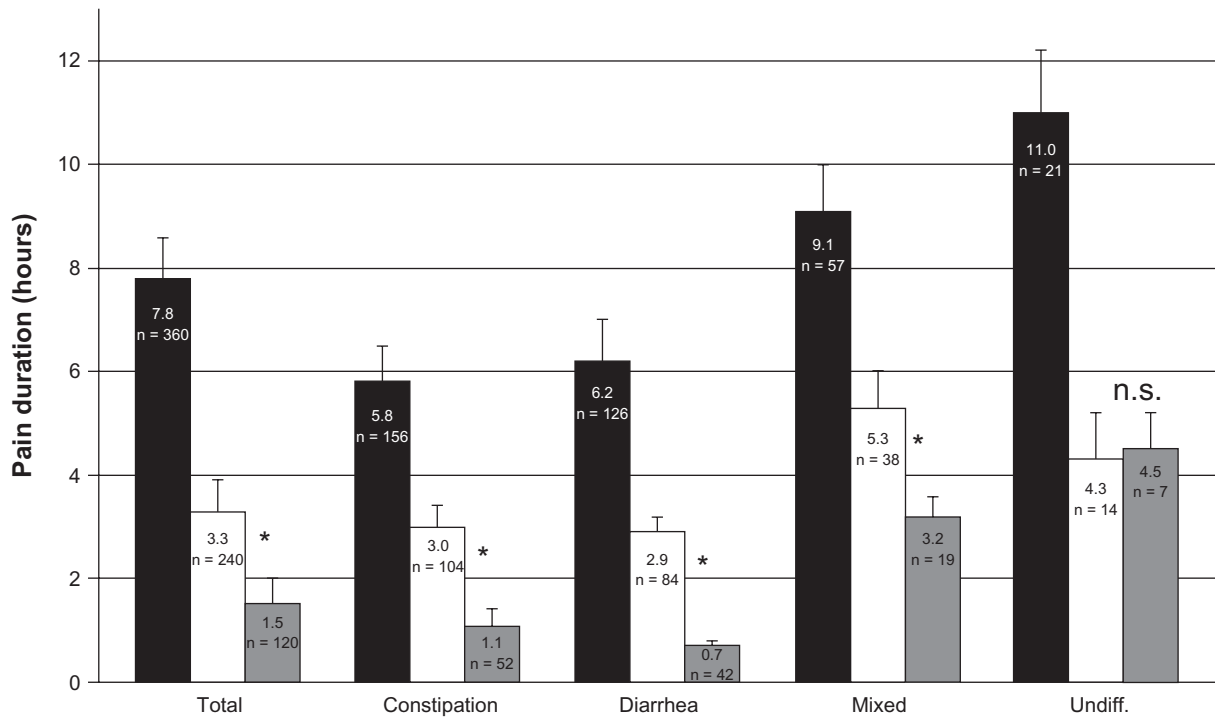


Figure 6 Pain duration (hours per day) in patients with different categories of IBS (constipation, diarrhea, mixed and undifferentiated type). **Notes:** “Total” refers to the intention to treat population; columns with significant difference between control and mesalazine group are marked by * ($P < 0.05$); “n.s.,” not significant. Values before treatment are represented by black columns, control group values are in white columns, and values from the mesalazine group are in gray. Vertical bars represent standard deviations.

Abbreviation: IBS, Irritable Bowel Syndrome.

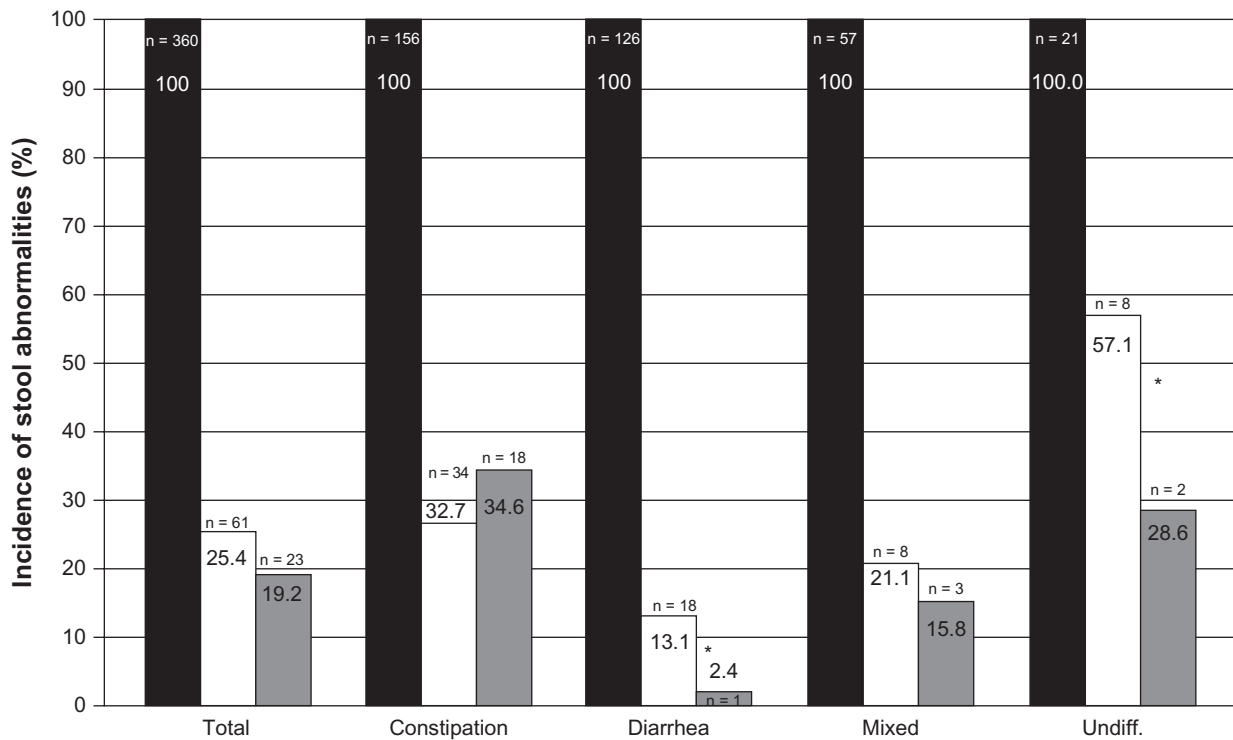


Figure 7 Incidence of stool abnormalities (%) in patients with different categories of IBS (constipation, diarrhea, mixed and undifferentiated type). **Notes:** "Total" refers to the intention to treat population; columns with significant difference between control and mesalazine group are marked by *($P < 0.05$). Values before treatment are represented by black columns, control group values are in white columns, and values from the mesalazine group are in gray. **Abbreviation:** IBS, Irritable Bowel Syndrome.

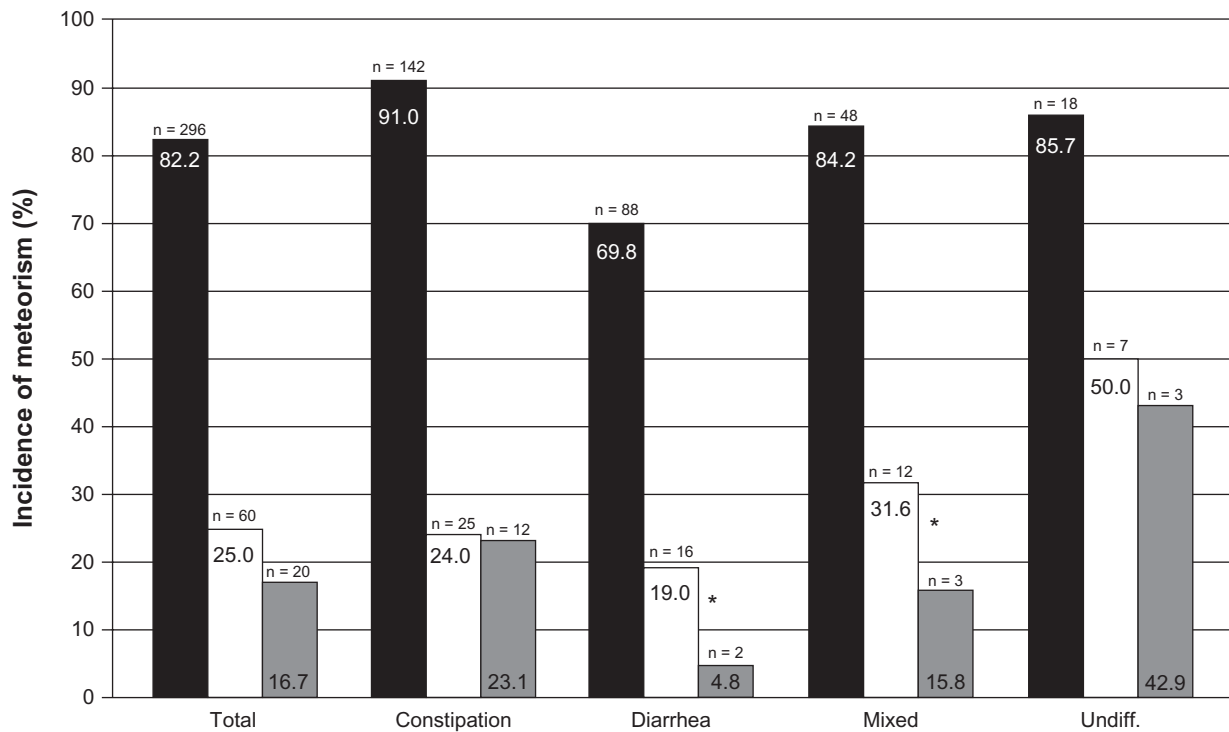


Figure 8 Incidence of meteorism (%) in patients with different categories of IBS (constipation, diarrhea, mixed and undifferentiated type). **Notes:** "Total" refers to the intention to treat population; columns with significant difference between control and mesalazine group are marked by *($P < 0.05$). Values before treatment are represented by black columns, control group values are in white columns, and values from the mesalazine group are in gray. **Abbreviation:** IBS, Irritable Bowel Syndrome.

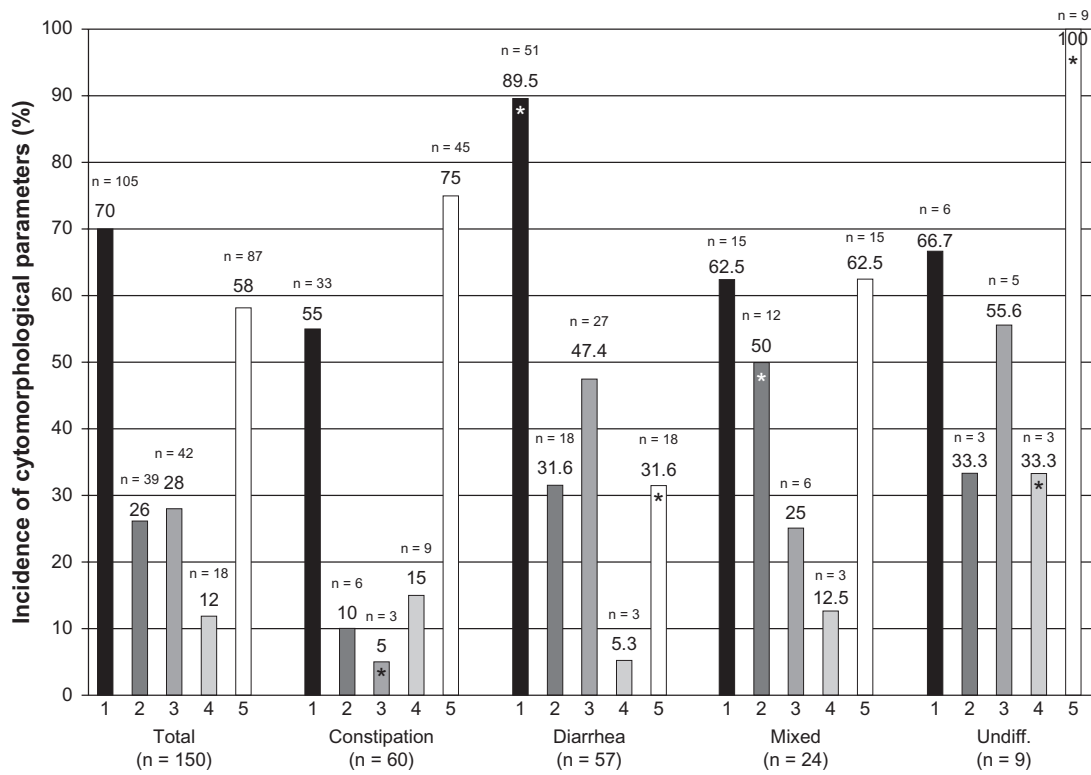


Figure 9 Incidence (%) of cytomorphologic parameters in patients with different categories of IBS (constipation, diarrhea, mixed and undifferentiated type). **Notes:** Only those parameters are represented where significant differences occurred between the total group and the individual categories. 1 – Pavement epithelial cells without changes, 2 – Columnar epithelial cells, 3 – Epithelial cells with degeneration, 4 – Nuclear polymorphism in epithelial cells, 5 – Mixed bacterial flora; columns with significant difference are marked by *($P < 0.05$). **Abbreviation:** IBS, Irritable Bowel Syndrome.

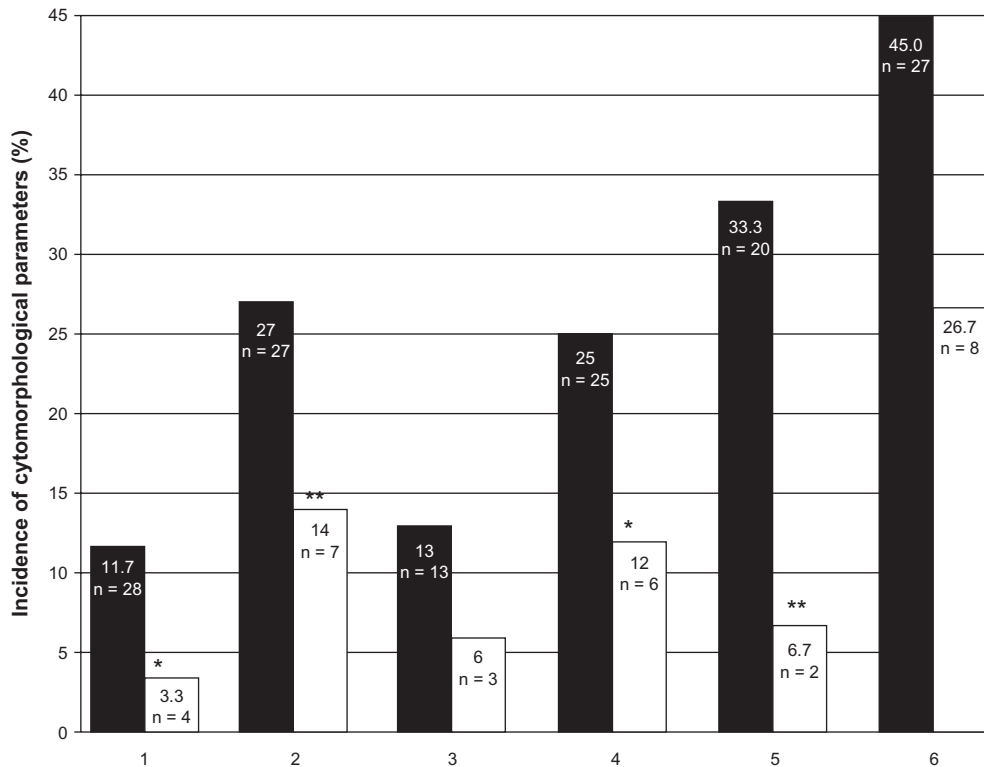


Figure 10 Incidence of cytomorphologic parameters after 28 day of treatment with mesalazine (white columns) compared with controls (black columns). **Notes:** 1 – Colon mucus changes, 2 – Cytological or histological changes, 3 – Epithelial cell degeneration, 4 – Singular leukocytes or macrophages, 5 – Mild cell infiltrations, 6 – Mucus production; columns with significant difference are marked by *($P < 0.05$) and **($P < 0.01$) respectively.

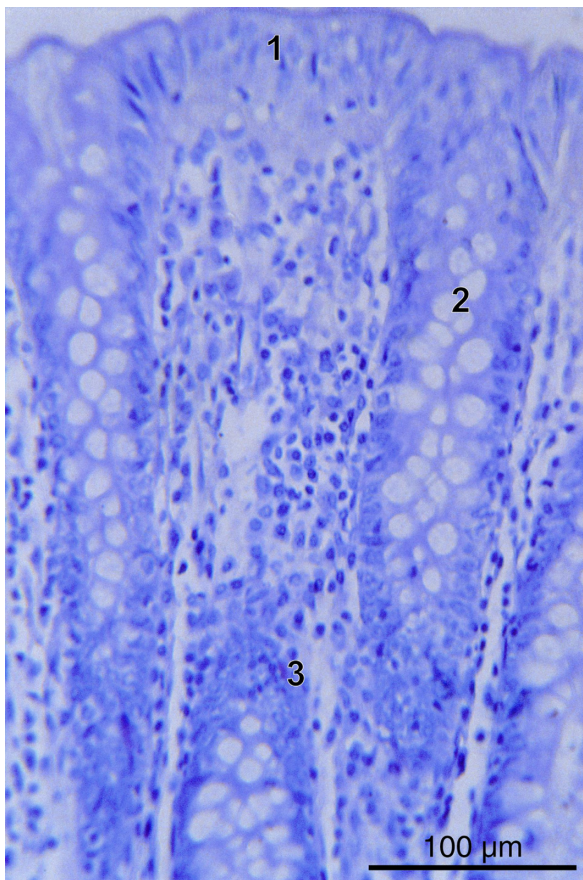


Figure 11 Colon mucosa of IBS patient (1 – columnar epithelium, 2 – goblet cells, 3 – endocrinocytes, hematoxylin-eosin staining, bar = 100 μm).
Abbreviation: IBS, Irritable Bowel Syndrome.

The pharmacological treatment of IBS is still controversial, due to the lack of knowledge about causal interdependencies. A plethora of drugs has been suggested for treatment of diarrhea, constipation and abdominal pain in IBS, but most treatments help only in a selected cohort of patients, and a significant and convincing success is still missing.^{2,12} That is

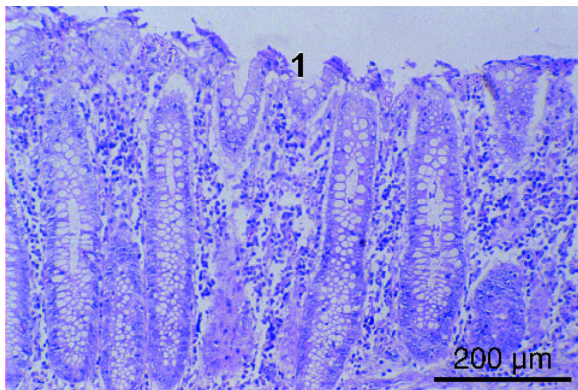


Figure 12 Flattening of superficial epithelium (1) in colon mucosa in IBS patient (hematoxylin-eosin staining, bar = 200 μm).
Abbreviation: IBS, Irritable Bowel Syndrome.

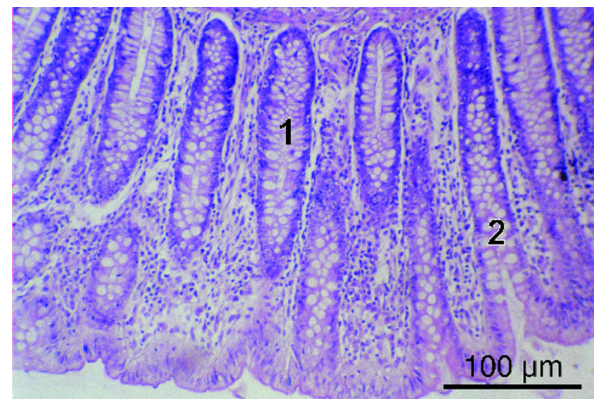


Figure 13 Goblet cells (1), crypts (2) in colon mucosa in IBS patient (hematoxylin-eosin staining, bar = 100 μm).

Abbreviation: IBS, Irritable Bowel Syndrome.

why Barbara et al recently concentrated on the importance of immune activation in the context of IBS.¹² Several studies seem to corroborate the hypothesis that immune activation may contribute to symptom generation in IBS patients.²⁴⁻³² Consequently the Barbara group initiated a “proof of concept” study to investigate the efficacy of mesalazine, a candidate well known and established as a remedy for inflammatory bowel diseases like ulcerative colitis and Crohn’s disease.³³ They found that mesalazine markedly reduced

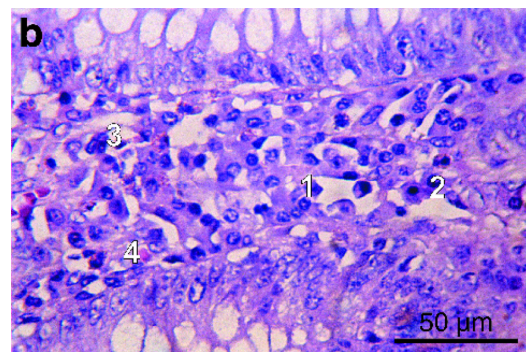
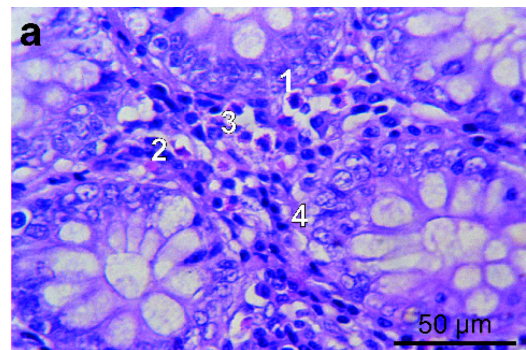


Figure 14 Cell infiltrations **A**) and edema **B**) in colon mucosa in IBS patient (1 – plasmocytes, 2 – lymphocytes, 3 – eosinophils, 4 – fibroblasts, hematoxylin-eosin staining). Bars = 50 μm.

Abbreviation: IBS, Irritable Bowel Syndrome.

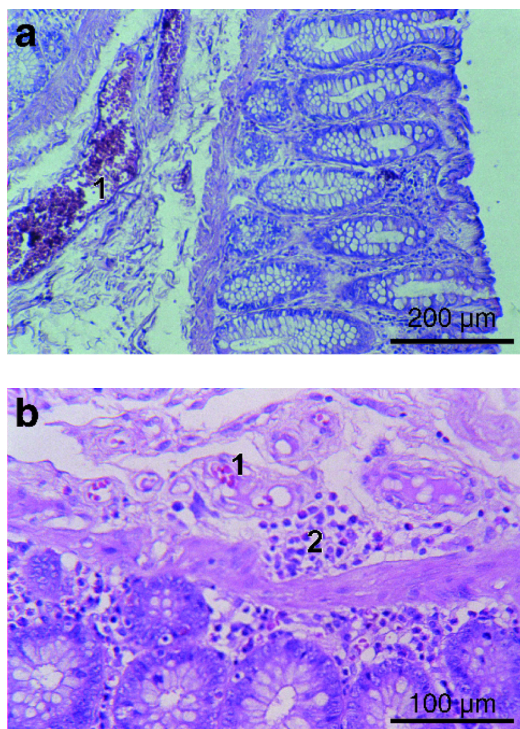


Figure 15 Plethora of microcapillaries **A**) and areas of cell infiltrations in the submucous layer of the submucosa **B**) of IBS patient (1 – microcapillaries with venous stasis phenomena, 2 – plasmocytic infiltrations, hematoxylin-eosin staining). Bars: a = 200 μm , b = 100 μm .

Abbreviation: IBS, Irritable Bowel Syndrome.

mucosal immune cells, especially mast cells, and significantly improved general well-being.³⁴ In contrast to our own findings that abdominal pain was reduced significantly in all categories of IBS, this study did not demonstrate a significant effect on pain and bowel habit. Moreover, in our study, the incidence of meteorism and stool abnormalities was reduced significantly at least in some of the IBS subtypes. Concerning indications of inflammatory and immune-related events, however, we could not find significant traces of abnormalities which could account for immune activation as a basis for IBS symptoms.

5-ASA was selected as a treatment for IBS because of the evidence of morphological signs of inflammation. Probably the presence of latent inflammatory processes in colon mucosa can explain the long-term recurrence of IBS with resistance to standard IBS treatments. 5-ASA is an anti-inflammatory drug. The mechanism of action aims at the inhibition of metabolism of arachidonic acid (predominantly the lipoxygenase pathway). In contrast, rifaximine is an antibiotic, effective in cases of manifest colon infections like post infectious IBS and bacterial overgrowth syndrome that may occur as an exacerbation of IBS.

At the same time, mucosal micro-inflammation in IBS can be a result of impact on visceral innervation, and an imbalance of serine/histamine. Amine precursor uptake decarboxylase (APUD) peptides are not related to infections. Hence, in our opinion, mesalazine is better suited for basic treatment of IBS considering the main pathogenetic mechanisms.

Conclusion

Mesalazine is effective in reducing abdominal pain in patients with different types of IBS. The duration of pain is also reduced significantly by treatment with mesalazine. Moreover, meteorism and abnormal stool pattern are improved significantly in some subtypes of IBS.

Acknowledgments

For preparation of the manuscript, editorial assistance was provided by the editorial office of medicaltext.de, Königswinter, Germany, on behalf of Dr Falk Pharma GmbH, Freiburg, Gemany.

Disclosure

The study was carried out on the sole responsibility of AED as a professor of the National Medical University of Donetsk and the Gastroenterological Center of Poltava Hospital Clinic, Poltava, Ukraine, and at the exclusive expense of the three participating hospitals. There was no conflict of interest between the authors and the respective institutions. The authors declare that no financial or other conflict of interest exists in relation to the content of the article.

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