https://doi.org/10.31925/farmacia.2025.1.23 **ORIGINAL ARTICLE**

DROTAVERINE EFFICACY AND SAFETY IN PATIENTS WITH COLIC PAIN ASSOCIATED WITH IRRITABLE BOWEL SYNDROME-OBSERVATIONAL RETROSPECTIVE CLINICAL STUDY

DARIA ARINA GHEORGHE [1#], ALINA COVACI [2], ISABEL GHITA [3]*, CLAUDIA MARIANA HANDRA [4#], AISA LAUDAT [5], MIHAI NEGUTU [6], MARINELA CHIRILA [7], LIANA GHEORGHE [1]

[1]*Department of Gastroenterology and Hepatology, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[2]*Department of Pharmacology, Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[3]*Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[4]*Department of Occupational Medicine, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[5]*Biofarm S.A., Bucharest, Romania*
[6]*ATI, Elias Hospital, Bucharest, Romania*
[7]*Medimun Consult SRL, Bucharest, Romania*

**corresponding author: isabelghita@yahoo.co.uk*
[#]*Authors with equal contribution.*

Manuscript received: October 2024

Abstract

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain and altered bowel habits without specific organic pathology. This study aimed to assess the efficacy and safety of drotaverine in patients with IBS. A multicenter, retrospective study analysed records of 200 IBS patients. Group A (n = 100) received Drotaverine (Antispasmin® Forte 80 mg Biofarm, Romania, 3 times daily for 14 days), and Group B (n = 100) followed a proper diet without medication. Efficacy parameters included pain relief, stool frequency, and improvement in general condition. Safety was assessed by adverse events and clinical evaluation. After 2 weeks, pain severity scores significantly decreased in 50 patients treated with Drotaverine compared to 32 controls ($p < 0.05$). After 4 weeks, 80 treated patients showed improvement in pain severity score *versus* 37 controls ($p < 0.05$). Mild adverse events occurred in 5 patients. Drotaverine significantly improved IBS symptoms without major adverse events.

Rezumat

Sindromul de colon iritabil (IBS) este o afecțiune gastrointestinală funcțională caracterizată prin dureri abdominale și modificări ale tranzitului intestinal, fără o patologie organică specifică. Acest studiu multicentric, retrospectiv a evaluat eficacitatea și siguranța drotaverinei la 200 pacienți cu IBS. Grupul A (n = 100) a primit Drotaverină (Antispasmin® Forte 80 mg Biofarm, Romania, de 3 ori pe zi, 14 zile), iar Grupul B (n = 100) a urmat doar o dietă adecvată patologiei. Parametrii de eficacitate au inclus evaluarea ameliorării durerii, frecvenței scaunelor și a îmbunătățirii stării generale. Siguranța a fost evaluată prin cuantificarea evenimentelor adverse și evaluarea statusului clinic. După 2 săptămâni, scorul de severitate a durerii abdominale a scăzut semnificativ la 50 pacienți tratați cu Drotaverină comparativ cu 32 pacienți din grupul de control ($p < 0,05$). După 4 săptămâni, 80 pacienți tratați cu drotaverină au prezentat o scădere a scorului de severitate a durerii față de 37 pacienți din grupul de control ($p < 0,05$). 5 pacienți au raportat evenimente adverse ușoare. Drotaverina a diminuat semnificativ simptomele IBS fără evenimente adverse majore.

Keywords: irritable bowel syndrome, drotaverine, efficacy, safety

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder. Abdominal pain and altered bowel habits in the absence of specific organic pathology represent two of the most common characteristics of this syndrome [1-4].

Abdominal pain can be a challenge, and differential diagnosis can include also colon cancer [5] or ulcerative colitis [6].

IBS prevalence is estimated at 3.7%-22% using Rome criteria [7-11]. In the US, prevalence is 10%-20%, with an incidence of 1%-2% per year [10, 12]. 75% of IBS patients seek medical advice for abdominal pain or discomfort [8, 13, 14].

Abdominal pain is traditionally linked to smooth muscle spasm, making antispasmodics the primary treatment. Management also involves dietary changes and stress relief [12, 15-22].

Antispasmodics remain the first-line therapy [23, 24]. Drotaverine, a musculotropic antispasmodic, is effective in IBS by relaxing gastrointestinal muscles, relieving pain, and improving transit.

There is paucity of data regarding uses of drotaverine in alleviating the pain and overall symptoms of IBS [25-31].

In recent decades, there has been a growing interest in evaluating and developing new or alternative treatment options, aiming to reduce medical costs and minimize research risks [32, 33].

The present study aimed to evaluate the efficacy and safety of Drotaverine (Antispasmin® Forte 80 mg, Biofarm, Romania) in IBS patients with abdominal colic pain.

The originality of this work lies in analysing individual IBS symptoms (abdominal pain, bowel habit changes, stool consistency, and defecation disorders) in the Romanian population. Mild IBS cases are often overlooked, and patients frequently self-medicate without consulting general practitioners. By involving GPs, this study also sought to raise awareness of IBS. Additional therapeutic effects and adverse reactions not listed in the product information were explored.

The primary objective was to assess the improvement in colic pain following oral drotaverine for up to 14 days, compared to baseline and a non-treatment group. A correlation was sought between pain severity/ location (clinically, by lab tests, and ultrasound) and treatment response based on dose and duration.

The secondary objective was to assess treatment safety through adverse event monitoring, laboratory analysis, ultrasound evaluation, and clinical observation.

According to the European Medicine Agency, the inclusion of an active comparator can currently not be recommended, but may become adequate in the future, once a "standard pharmacological therapy" is established [34].

Materials and Methods

Study design

This was a multicentre, retrospective observational study evaluating data from general physicians from 30 medical centres in Romania. The study covers data reported during the period 2019 - 2022.

Ethical approval

The study started only after the approval of the National Bioethics Commission was obtained. The study was performed in compliance with the applicable ethical standards (Declaration of Helsinki). The patients included in the study provided the informed consent prior to participation to the study.

Study population

The study included patients that were registered on the lists of general practitioners for at least 5 years.

The data set evaluated consisted of records from 609 patients with abdominal pain with different localizations. The records showed that patients were diagnosed with IBS, dysmenorrhea or renal colic. Out of 609 patients, there were 203 patients diagnosed with IBS but 200 patients were selected based on the inclusion and exclusion criteria below and included in the study as follows: Group A (n = 100) included patients treated with drotaverine 80 mg tablet 3 times daily, 1 hour before meal, and Group B (n = 100) included patients that received no treatment but only adequate diet.

The population in the treated and non-treated group were matched for confounders (age and sex).

Inclusion criteria

Patients with symptoms that met the Rome II diagnostic criteria for IBS [2], 18-80 years old patients, non-smoking, male and women, patients with blood test and liver function tests in the normal range.

Exclusion criteria

Patients with one or more of the following conditions: pregnancy, any acute or chronic conditions during the acute exacerbation period, any infectious-contagious diseases until the end of mandatory isolation period, repeated, profuse bleeding, upper digestive bleeding, confirmed haematological and neoplastic diseases, neurological diseases or recent cranio-cerebral trauma, exacerbated mental disorders, drug addictions, chronic alcoholism, hypertension not controlled by medication, organ failure (heart, liver, kidney), advanced liver diseases (chronic hepatitis, cirrhosis with ascites), decompensated pancreatic disorders, advanced chronic kidney disease (creatinine >3 mg/dL), uric nephropathy, decompensated type II diabetes, obesity with cardiorespiratory failure, immobilized patients, vagotomy or partially/totally resected stomach with anastomoses, suspicion of oesophageal-gastro-intestinal neoplastic diseases: involuntary weight loss with lack of appetite, decreased appetite for meat products, frank digestive bleeding (hematemesis, melena) in the past, iron deficiency anaemia without an obvious cause, active gastric/duodenal ulcer, suspicion of conditions accompanied by malabsorption (celiac disease), conditions known as food intolerances (to lactose, egg proteins, fish, nuts, sesame, etc.), significant dysphagia for liquids, idiopathic inflammatory bowel diseases (Crohn's disease, ulcerative colitis) in personal history, treatments with antibiotics, antidiarrheals, triptans (antimigraine medication), patients on treatment with Sintrom® type oral anticoagulants (acenocoumarol), uncontrolled monthly INR. The patients did not receive any other nutritional supplements [30] or medication with an analgesic effect or any other antispasmodic medication

which could have influenced the drotaverine efficacy. Patients with nicotine addiction were also excluded due to nicotine enzyme induction effect and possible interference with the treatment [28].

Study interventions

The product under investigation was Drotaverine (Antispasmin® Forte tablets 80 mg Biofarm, Romania) administered as one 80 mg tablet 3 times a day, one hour before meal for no more than 14 days. All patients followed the medical treatment at the indication of the attending physician following a colic episode. All patients followed the medical treatment at the indication of the attending physician following a colic episode. Treatment adherence was assessed through patient self-reporting at each follow-up visit. The medical emergencies reported during drug treatment were treated according to the protocols approved by the Ministry of Health. Patients continued to receive their underlying medication (such as antihypertensives under the conditions of measuring blood pressure twice a day, diuretics, antidiabetic medication with oral antidiabetics or insulin under the conditions of measuring blood sugar three times a day).

The control group received recommendations and followed a standard diet for IBS (according to the local guidelines, the diet is the one recommended in case of gastritis). Adherence to dietary recommendations was assessed through patient self-reports at follow-up visits.

Study procedure

Outline baseline evaluation and follow up visits schedule

As part of general clinical practice, the patients were regularly consulted (minimum 4 visits per month) on an outpatient basis in individual medical offices. The patients presented themselves to the attending physician at the end of each week, for 1 month.

The patients included in the study have completed specific data regarding the severity and frequency of abdominal pain or intestinal transit in their own daily diary.

The evaluations were carried out by the general practitioners as part of their usual, general medical practice. The data was collected considering the following visits: E0 - Initial visit (assessment). Completing preliminary patient data (laboratory tests, ultrasound, medical history, objective physical examination); E1 - Treatment prescription. Clinical and laboratory analyses. Determination 1 (laboratory tests, ultrasound, medical history, objective physical examination); E2 - Evaluation at the end of the 7 days of treatment. Clinical and laboratory analyses. Determination 2 (laboratory tests, ultrasound, medical history, objective physical examination); E3 - Evaluation was carried out at the end of the 14 days of treatment. Determination 3 (laboratory tests, Echo, history, objective physical examination); E4 - Evaluation was carried out 1 week after the end of the treatment. This evaluation was carried out daily by completing a telephone questionnaire that referred to the symptoms associated with each patient; E5 - Evaluation carried out 2 weeks after the end of the treatment.

Primary outcome

The efficacy parameters evaluated were pain relief (in terms of severity and frequency), stool frequency and overall global improvement in patient's complaints. Abdominal pain has been quantified using 5 specific validated scales as further described.

Pain severity score was registered by physician using scale adapted from standard clinical pain assessment tools by Jensen in 2003 as presented below: None - score 0; Mild - score 1; Moderate - score 2; Severe - score 3. Definitions: Mild: self-limiting, does not require medication, does not interfere with normal daily activities; Moderate: not self-limiting, requires medication, but does not interfere with normal daily activities; Severe: not self-limiting, requiring medication that provide relief, interrupting normal activities [35].

Pain severity score was registered also by patients using Visual Analog Scale (VAS for pain) [36]. The severity of the pain was questioned about also by the attending physician in terms of severity (mild, moderate, and severe) and was evaluated as points (scale between 1-10).

Pain intensity was registered by the patient on the 11-point PI-S (Pain Intensity score), categorized from 0 = no pain to 10 = worst possible pain. This approach is in line with the Pain Intensity Score (PI-S), widely validated for clinical and research settings [37].

Pain frequency was recorded by the patient as number of pain episodes registered in different moments of the study. This method of event-based pain frequency recording is often applied in clinical trials evaluating abdominal disorders

Pain relief was evaluated on an 11-point numerical rating scale categorized from 0 = no relief to 10 = complete relief. The main efficacy parameter was pain relief expressed at different moments of the study. This type of pain relief scoring is frequently employed in pain management research to capture treatment efficacy [38].

Assessment of *stool characteristics* was done by registering the characteristics and the frequency of stool (once or twice daily - score 0; none or at least three times daily - score 1). This scoring system is consistent with clinical practice evaluating the functional gastrointestinal disorders and aligning with the Rome IV diagnostic framework for bowel pattern abnormalities [39].

Patient's and investigator's global evaluation efficacy was recorded at the end of therapy using a 5-point scale (Likert scale: 0 = poor; 1 = fair; 2 = good; 3 =

very good; 4 = excellent). This Likert-type scale is a validated approach for measuring global satisfaction and perceived treatment efficacy in clinical trials [40].
Physicians have also used a pain-scale to evaluate if the therapy relieved the abdominal pain and improved the patient's Quality of Life, in line with standard practice for evaluating pain outcomes in gastrointestinal disorders [11].
Combining both patient-reported outcomes (PRO) and clinician evaluations is an established practice in trials involving chronic pain and gastrointestinal conditions to ensure a more comprehensive understanding of treatment effects [41].
A change of ≥ 2 points was considered clinically meaningful, as suggested by standards for symptom relief and treatment satisfaction in functional gastrointestinal disorder research [42]. The patient's evaluation reflected their perception of improvement, while the clinician's evaluation integrated patient feedback and clinical observations.

Secondary outcome

The secondary outcome was safety. The safety parameters evaluated were adverse reactions (ARDs) self-reported by the patients, clinical and laboratory parameters such as blood count, ALT, AST, uric acid, creatinine, cholesterol, triglycerides, bilirubin and blood sugar level where available. The ADRs as reported by the patients and clinical and laboratory test results were collected and evaluated for intensity and causality to the study treatment. The intensity of ADRs was classified as severe, moderate, and mild according to WHO definitions for severity:
Severe: an ADR that results in significant disability, requires hospitalization, or is life-threatening or fatal.
Moderate: an ADR that causes a temporary interruption in treatment or requires a change in the drug dose but does not result in permanent harm or significant disability.
Mild: an ADR that does not interfere with the patient's ability to continue treatment and causes minimal discomfort or inconvenience, with no significant medical consequences.

Statistical Analysis

The statistical analysis was used to compare the changes in symptoms between the drotaverine treated patients and the untreated group at the end of the 1st, 2nd, 3rd, and 4th week.
The statistical analysis included also parameters such as: age, living environment, sex, height, weight, BMI, situation regarding the years of study, profession, employee/retired, pre-existing conditions, operations, concomitant treatment. In addition, the treatment adherence (the total number of medicinal treatments compared to the maximum number of indicated administrations), adherence to the administration of a standard diet and additional meals throughout the day were monitored. Data was entered into Microsoft Office Excel and analysed using SPSS software. The Mann - Whitney U-test (two-tailed) was used to compare the changes in symptom score between drotaverine and the untreated groups at 2nd, 3rd, and 4th weeks. Wilcoxon signed ranks test and McNemar tests were used for paired data to test the changes in the symptoms score between baseline and 2nd, 3rd, and 4th weeks. A $p \leq 0.05$ was considered statistically significant.
The comparison of continuous variables (e.g., pain severity score, frequency of colic episodes) between treated and untreated groups was performed using descriptive statistics and the appropriate parametric tests for between-group comparisons. The comparison of categorical variables (e.g., presence of constipation, diarrhoea, bloating) and the frequency of improvement or symptom relief across groups were analysed using percentage-based comparisons and tested for statistical significance. For continuous variables, changes over time were assessed through repeated measures or comparisons at different evaluation points (*e.g.*, baseline, day 3, week 4). A p-value of < 0.05 was considered statistically significant, and where indicated, the significance was marked on the figures (*e.g.*, $p < 0.01$ or $p < 0.05$).

Results and Discussion

Data set consisted of records from 609 patients presenting with abdominal pain. Following initial evaluation of data, records from 200 patients met the inclusion criteria and were therefore selected and analysed.
The patients were divided into 2 groups, Group A included 100 patients treated with 1 tablet of drotaverine 80 mg, 3 times daily, 1 hour before meal and Group B included 100 patients that received no treatment but only adequate diet.
The drotaverine group *vs.* non-treated group were well balanced regarding the baseline symptoms.
After 7 days of treatment, 15 patients from the Group A (treated group) withdrew from the study. These patients stopped taking the medication because they no longer had symptoms specific to the disease.
Another 24 patients from the Group B (untreated group) withdrew from the study in the first 3 days of the study without having a certain objective reason.
Therefore, 85 patients in the treated group and 76 patients in the untreated group completed the study (see Table I).

Demographic data

With regards to subjects' age, initially the treated group consisted of 35 people with ages between 30 - 40 years old, 51 people with ages between 40 - 50 years old, 10 subjects with age between 50 - 60 years old, 4 people with ages between 60 - 70 years old (Figure 1).

Table I

Demographic data of patients

	Drotaverine group (*n* = 100)	Untreated group (*n* = 100)
Patients Included in study	**100**	**100**
Patients Evaluable 1st week	**100**	**76**
Patients Excluded after first week	**15** (after 7 treatment days)	**24 (after 3 days)**
Patients Evaluable after 2end week	**85**	**76**
Patients Evaluable after 3th week	**85**	**76**
Patients Evaluable after 4th week	**85**	**76**
Patients included in study and diagnosticated with different type of Irritable Bowel Syndrome at the beginning of the study		
Type C	**41**	**44**
Type D	**32**	**22**
Type M	**27**	**34**
Mean Age (yr)	**43.3 ± 17**	**51 ± 8**
Gender (Male: female)	**2:10**	**1:9**
Rural-to-Urban Area	**1:3**	**1:3**

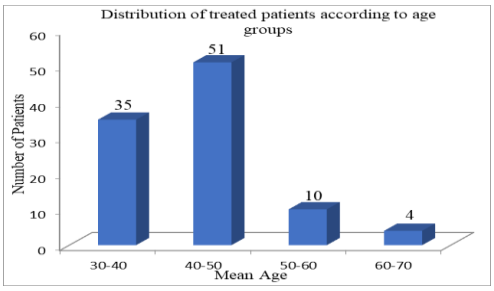


Figure 1.

Distribution of treated patients according to age groups at E1 visit

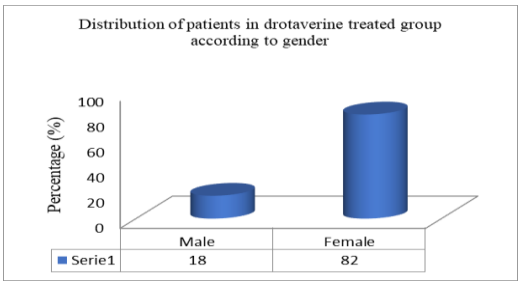


Figure 3.

Distribution of treated patients according to gender group at E1 visit

The minimum age was 30 years old, while the maximum one was 70 years old. Regarding the age distribution, the study group was homogenous, as shown by the statistical analysis of the data. There was a higher number of female subjects (82%) than male subjects (18%), which can be easily explained by the fact that IBS is more frequent in women than males (Figure 2, Figure 3).

The incidence of IBS symptoms remained consistent (significantly higher in women than in men.

Urban/rural distribution is presented in Figure 4, where 74% of the patients came from the urban environment and the remaining 26% from the rural environment.

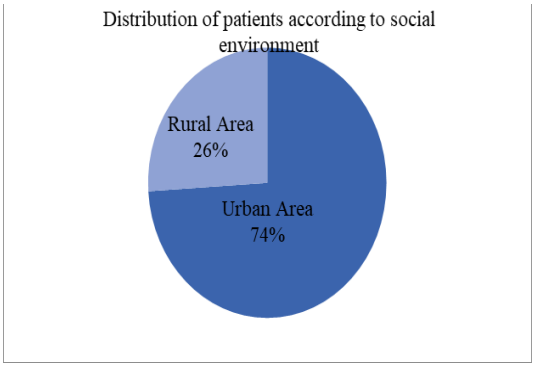


Figure 4.

Distribution of patients according to social environment at E1 visit

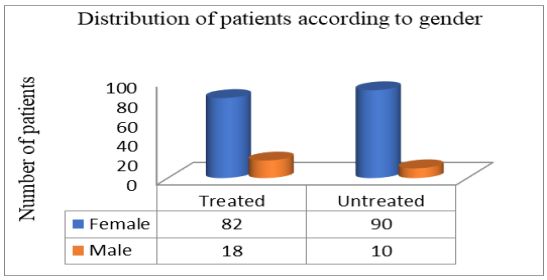


Figure 2.

Distribution of patients according to gender at E1 visit

Adherence to the treatment

At beginning of the second week, 85% of the patients treated with drotaverine were adherent to the treatment, while 15% stopped the treatment after the first week (Figure 5).

59% of the total number of patients of group B were adherent to the diet during the 14 days, while 41% stopped the diet restrictions after the first week (Figure 6).

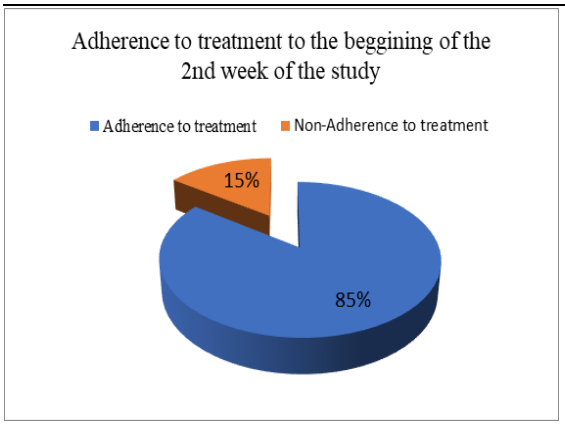


Figure 5.
Adherence of treatment (percentage of treated patients)

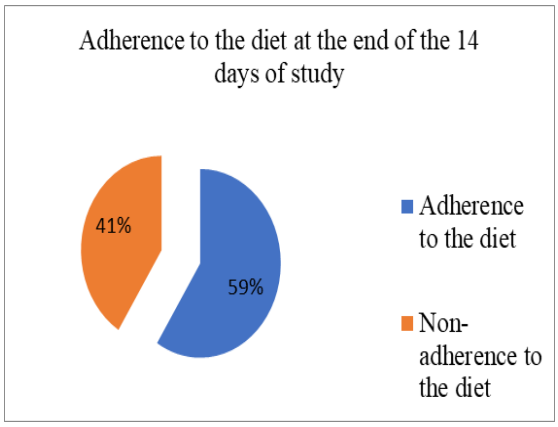


Figure 6.
Adherence to diet after 2 weeks (percentage of patients)

Efficacy results

The symptoms evaluated were the ones documented from the assessment visit until the completion of 4 weeks. 167 of the patients presented severe-moderate abdominal pain at the E1 visit, while 33 patients presented only a mild abdominal pain at the beginning of the treatment (Figure 7).

Among the patients who belonged to the treated group, at the beginning of the 3 days of evaluation period, 90 had abdominal pain of severe-moderate intensity, and 10 had mild abdominal pain. Among the untreated patients, at the beginning of evaluation period, 77 had abdominal pain of severe-moderate intensity, and 23 had mild abdominal pain (Figure7).

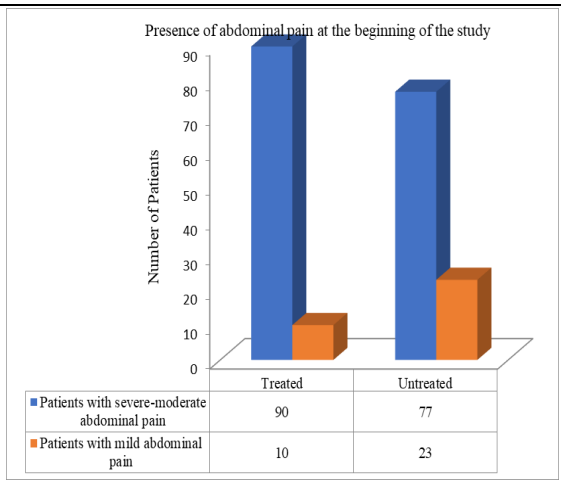


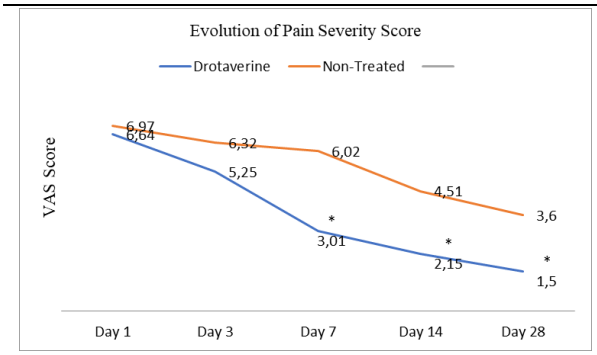
Figure 7.
Presence of abdominal pain at the beginning of the study

The pain severity score decreased from 6.64 to 5.25 on day 3 in the drotaverine group compared to group B where the score reduction was from 6.97 to 6.32 ($p < 0.01$). This reduction in pain severity continued until the end of the evaluation period. At the end of 4 weeks of evaluation, the pain severity score decreased in drotaverine group from 6.64 to 1.51 *vs.* non-treated group from 6.97 to 3.62. The difference between groups A and B was statistically significant ($p < 0.05$) (Figure 8A).

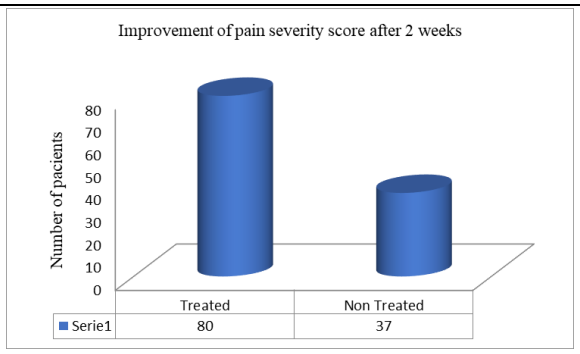
A reduction of over 5 points on a 10-point scale suggests a substantial clinical improvement in pain for treated patients. This is generally considered a clinically meaningful change, as a reduction of 2 - 3 points on a VAS scale is often seen as significant in pain studies. This outcome is both statistically and clinically significant.

With regards to the global evaluation of the improvement of abdominal pain as it was perceived by the patient and also as assessed by the clinician, VAS scale assessment was conducted at the beginning of the 3rd week and at the end of the evaluation period (after 4 weeks). 50 patients from the treated group perceived an improvement in pain in the beginning of the third week *vs.* 32 patients from untreated group (Figure 8 B).

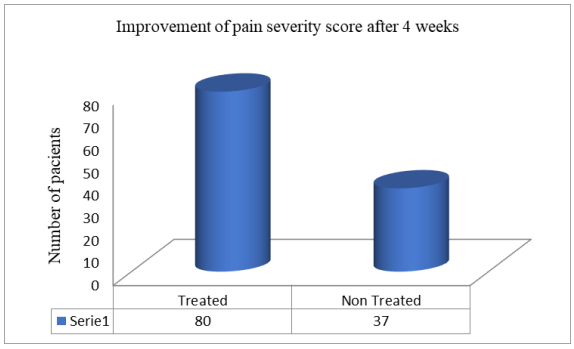
At the end of the fourth week, 80 treated patients perceived this improvement. This improvement was not registered in the same manner for the untreated group because, at the end of the study, only 37 of the untreated patients perceived a major improvement in the global relief in abdominal pain. (Figure 8C).



A



B



C

Figure 8.
A- Evolution of Pain Severity Score; B - Improvement of pain severity score after 2 weeks; C - Improvement of pain severity score after 4 weeks

From the clinicians' point of view, at the end of the 4 weeks of evaluation, only 70 treated patients registered an improvement in the perception of abdominal pain.

The frequency of abdominal pain was evaluated based on the recorded number of colic episodes in 24 hours. Intestinal colic was defined as a painful intestinal contraction with a variable duration between a few tenths of seconds and up to a few minutes. In the first week, the average number of colic episodes was 8 in treated group *vs.* 9 in untreated group. In the 2nd week, the colic episodes were reduced to 2 for treated group *vs.* 4 for untreated. In the 4th week, even if the patients stopped the treatment, the treated group had only 1 colic episode *vs.* 3 colic episodes for the untreated patients ($p < 0.05$) (Figure 9).

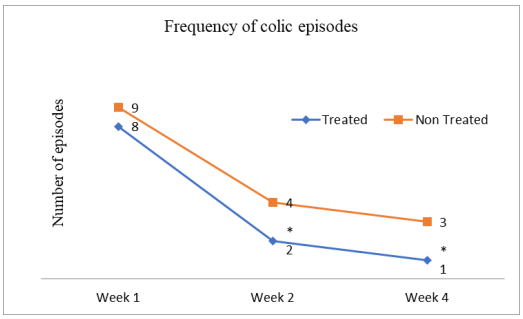


Figure 9.
Frequency of colic episodes

On the first day, 45 treated patients recorded 8 - 6 colic episodes, 35 patients recorded 6 - 5 episodes, 2 patients recorded 5 - 4 episodes, 10 patients recorded 4 - 2 colic episodes, and 8 patients recorded 1 episode. On the 3rd day, 22 patients recorded 8 - 6 episodes, 15 patients recorded 6 - 5 episodes, 3 patients recorded 5 - 4 episodes, and 7 patients recorded 4 - 2 episodes and only 2 patients recorded 2 episodes. On the 7th day, 5 patients recorded 8-6 episodes, 5 patients recorded 6-5 episodes, 2 patients recorded 5 - 4 episodes, and 1 patient recorded 4 - 2 episodes (Figure 10).

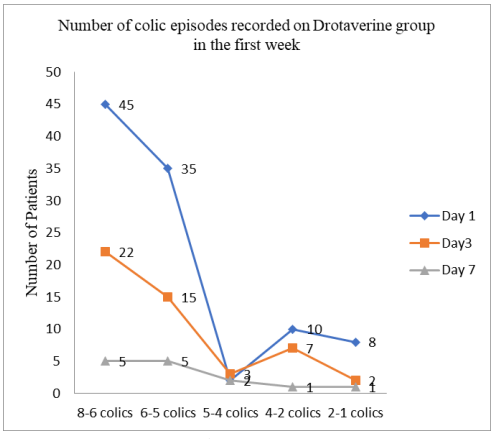


Figure 10.
Number of colic episodes recorded in the Drotaverine group

The results recorded on days 3 and 7 favoured the treatment compared to the results recorded in the untreated group. Patients who did not receive treatment recorded an increased number of colic episodes on days 1, 3, 7. Therefore, for the untreated group on day 1, 55 patients recorded 8-6 colic episodes, 35 patients recorded 6-5 episodes, 2 patients recorded 5 - 4 episodes, 6 patients recorded 4 - 2 colic episodes, and 2 patients recorded 2 - 1 colic episodes. On the 3rd day, 50 patients recorded 8-6 episodes, 33 patients recorded 6-5 episodes, 5 patients recorded 5 - 4 episodes, 7 patients recorded 4 - 2 episodes, and 5 patients recorded 2 - 1 episodes. On the 7th day, 17 patients recorded 8 - 6 episodes, 20 patients recorded 6-5 episodes, 21 patients recorded 5 - 4 episodes, and 18 patients recorded 4 - 2 episodes (Figure 11).

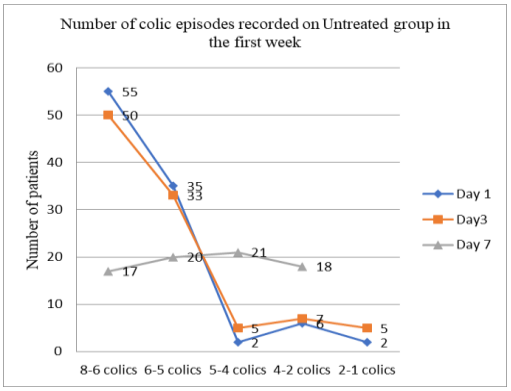


Figure 11.
Number of colic episodes in the untreated group

Reducing colic frequency from 8 episodes/day to 1 episode/day reflects significant symptom relief.
The pain frequency relief was also evaluated. At the end of the first week, in 74 patients belonging to drotaverine group recorded a decrease in pain frequency compared to 34 in non-treated group. This trend was observed also in the third week for 80 patients belonging to the drotaverine group vs. 36 belonging to the untreated group. In the 4th week, 81 drotaverine patients registered a decrease in pain frequency compared to 37 patients in the untreated group (Figure 12).

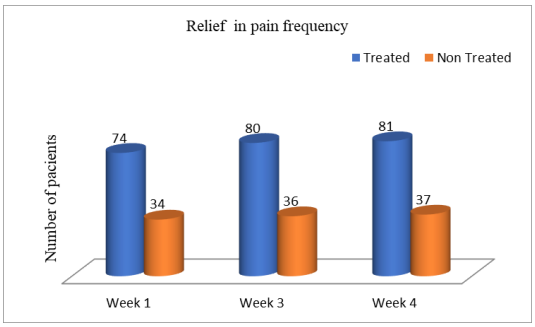


Figure 12.
Relief in pain frequency

An improvement in stool frequency occurred in 30, 36 and 47 of patients belonging to the group treated with drotaverine at the end of the 2nd, 3rd and 4th week, respectively, as compared with 7, 10 and 15 patients from untreated group (Figure 13).

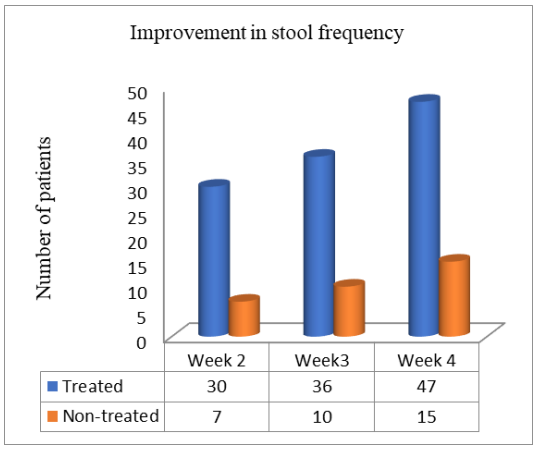


Figure 13.
Improvement in stool frequency

Regarding the intestinal transit (as it was perceived by the patient) a significant improvement in 60 patients in the drotaverine group at the end of evaluation was observed, as compared with improvement in 13 patients from untreated group (Figure 14).

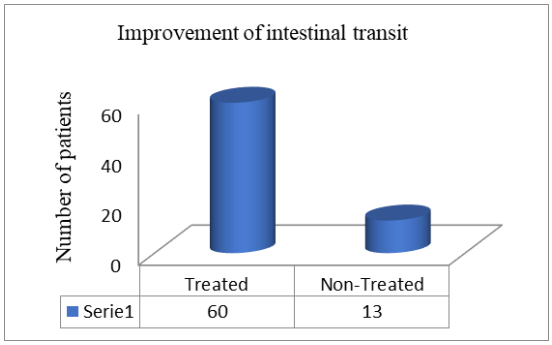


Figure 14.
Improvement of intestinal transit

Another recorded parameter was the presence of constipation. At the beginning of the evaluation, 40 patients in the treated group presented constipation compared to the 44 patients in the untreated group. After 2 weeks, only 30 patients from the treated group had constipation compared to 41 patients from the untreated group. At the end of the study, 29 patients in the group treated with drotaverine presented constipation, while in the untreated group 41 patients presented this symptom (Figure 15).

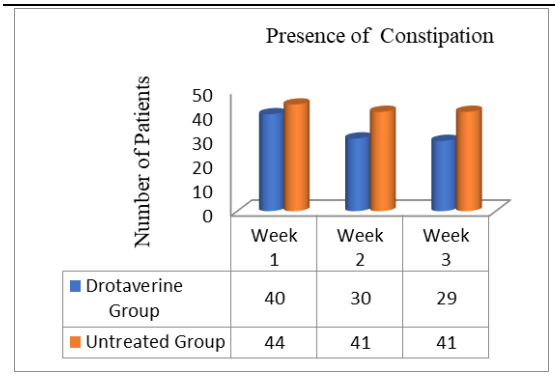


Figure 15.
Presence of constipation

The above data (Figure 15) showed that, during the 4 weeks of the evaluation period, there was an improvement in the presence of constipation, especially registered in the drotaverine group, but this improvement may also be due to the diet that the patients received.

Another recorded parameter was the presence of diarrhoea. The presence of diarrhoea at the end of the 4 weeks of evaluation, clearly improved in the case of the treated group. In the case of the group treated with drotaverine, in the first week, 32 patients presented diarrhoea, then, in the second week, the number of patients experiencing this symptom reduced to only 10 and at the end of the study only 8 patients presented diarrhoea. In the case of the untreated group, 22 patients had diarrhoea in the first week, 18 patients in the third week and 12 patients at the end of the evaluation period. The results are presented in Figure 16.

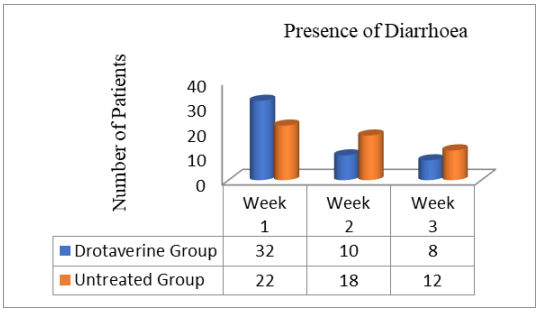


Figure 16.
Presence of diarrhoea

The most spectacular improvement of the intestinal transit occurred in patients treated with drotaverine that had IBS type M, all 27 patients improving their intestinal transit from the first week of treatment.

With regards to intestinal transit and stool consistency, while the numerical improvements are statistically significant, the clinical benefit is particularly notable in IBS-M patients, all of whom reported transit normalization from the first week. This supports the clinical utility of Drotaverine in patients with mixed bowel habits, a challenging IBS subgroup.

Another parameter recorded in our study was represented by the improvement of bloating. Bloating was present in 38, 29 and 28 patients respectively belonging to the drotaverine treated group in the first, third and fourth week *vs.* 40, 39 and 38 patients belonging to the untreated group (Figure 17).

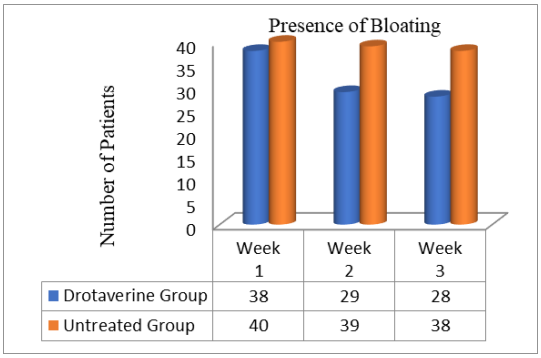


Figure 17.
Presence of bloating

While bloating improvements were modest, the general condition enhancement aligns with the overall symptom relief (pain, stool consistency, colic reduction), reflecting a clinically meaningful benefit. Regarding the improvement of the general condition, 40% of the treated patients noticed an improvement after the first week of treatment compared with 20 % for the untreated. In the second week, the general condition improved in 51% of the treated patients compared with 22% for untreated. Even if the treatment ended after 14 days, in the third week the general condition improved in 55% of the treated patients group compared with 30% for untreated. In the 4th week, it improved in 56% of the treated patients compared with 33% for untreated patients (Figure 18, Figure 19).

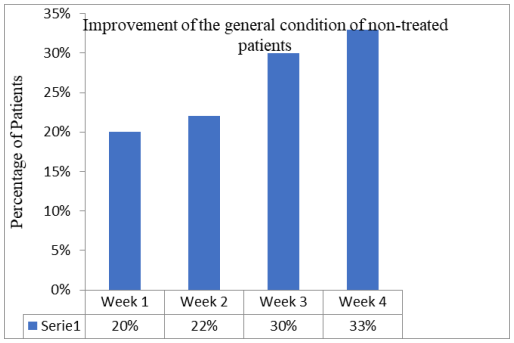


Figure 18.
Improvement of the general condition in non-treated patients

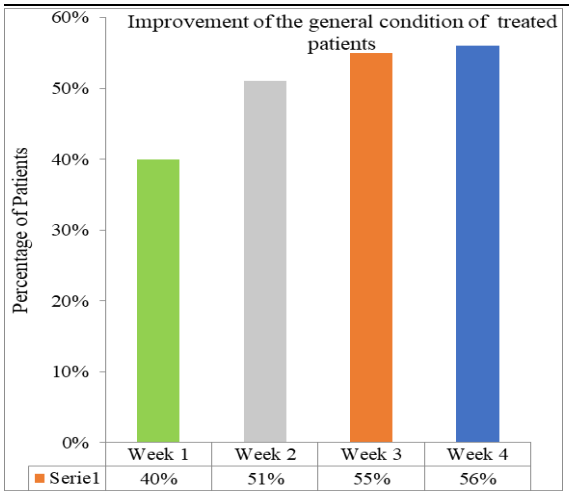


Figure 19.
Improvement of the general condition in treated patients

Patient-perceived improvement is a clinically important measure, especially in IBS, as subjective symptom relief often drives treatment success. This result supports the clinical relevance of drotaverine therapy.

Safety results

The adverse events for the treated group were evaluated. 5 patients in the drotaverine group reported mild adverse events. At the same time, these events were registered also for the untreated group, for 22 patients. All these 5 adverse events were of mild intensity, had a short duration and did not require discontinuation of therapy. All these adverse events are presented in Table II of them are digestive events - flatulence, bloating, constipation - with short duration and were registered on treated patients with IBS type M.

Table II
Incidence of adverse events after 10 treatment days

Adverse effect	Drotaverine (n = 5 patients out of 90 patients)	Untreated group (n = 22 patients out of 80 patients)
Hypotension	0	1
Palpitation	0	0
Headache	0	2
Sleep disorders	1	2
Generalized weakness	0	0
Chronic fatigue	0	1
Dizziness	1	3
Heartburn	0	2
Nausea	0	0
Flatulence	1	4
Bloating	1	2
Belching	0	2
Constipation	1	2
Diarrhea	0	1

Regarding the evaluation of haemoglobin values, as can be seen in the Figure 20, in the case of the patients who received drotaverine there were no statistically significant changes during the 4 weeks of evaluation, compared to the untreated group, the lowest average haemoglobin value being reported for the non-treated group (13.1g/dL).

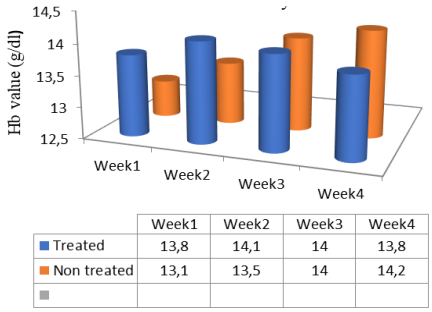


Figure 20.
Evolution of haemoglobin values during the 4 weeks of the study

The blood glucose value, as can be seen from Figure 21, in the case of the patients who received drotaverine, did not undergo statistically significant changes during the 4 weeks of evaluation, compared to the untreated group; the lowest average blood glucose value being 88 and the highest of 118 mg/dL.

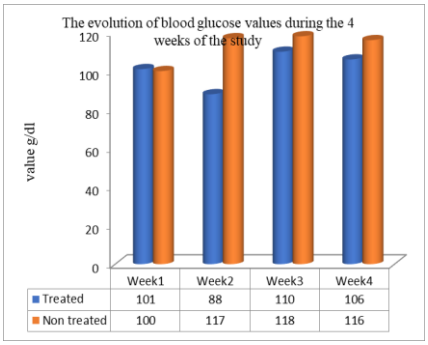


Figure 21.
Evolution of blood glucose values during the 4 weeks of the study

The blood urea value, as can be seen from Figure 22, in the case of the patients who received drotaverine also did not undergo statistically significant changes during the 4 weeks of evaluation, compared to the untreated group.

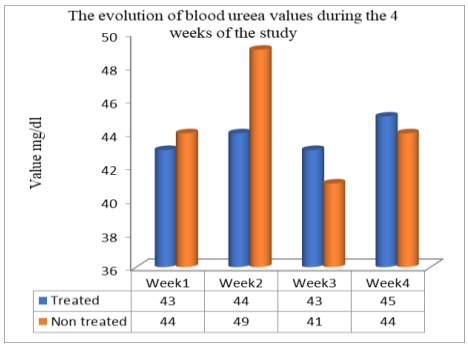


Figure 22.
Evolution of blood urea value values during the 4 weeks of the study

The blood creatinine value hasn't changed either. For the patients who received drotaverine, blood creatinine value did not undergo statistically significant changes during the 4 weeks of evaluation, compared to the untreated group (Figure 23).

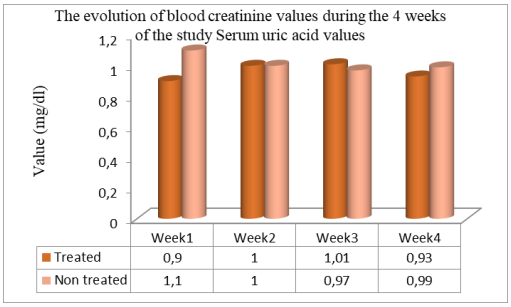


Figure 23.
Evolution of blood creatinine values during the 4 weeks of the study

Serum uric acid values did not undergo statistically significant changes in the case of the treated group compared to the untreated group throughout the 4 weeks of evaluation (Figure 24).

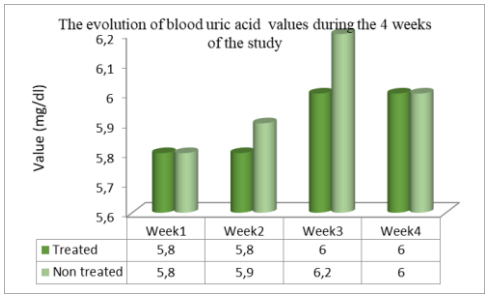


Figure 24.
Evolution of blood uric acid values during the 4 weeks of the study

There were no statistically significant differences between the evolution of ALT values between the treated group and the untreated group. The same was observed also in the case of AST values. (Figure 25, Figure 26).

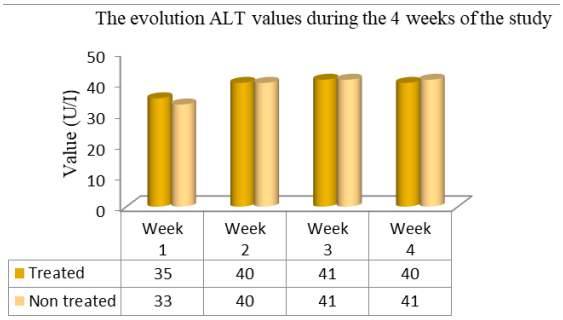


Figure 25.
Evolution of ALT values during the 4 weeks of the study

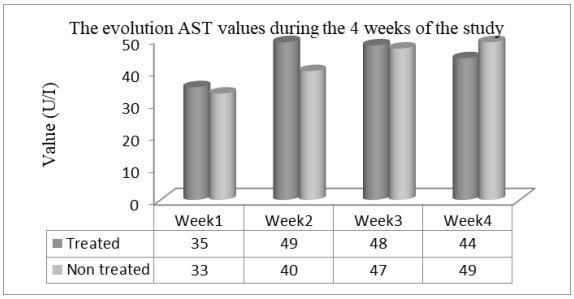


Figure 26.
Evolution of AST values during the 4 weeks of the study

After analysing the average cholesterol values during the 4 weeks of evaluation, it was concluded that there were no statistically significant differences between the 2 groups (Figure 27).

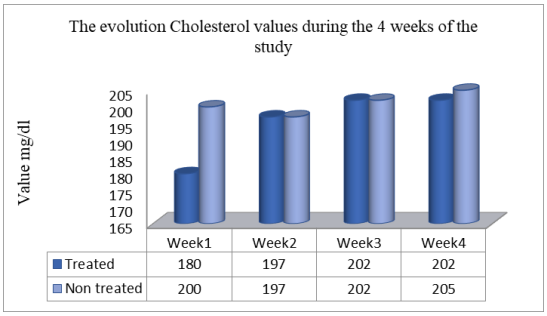


Figure 27.
Evolution of cholesterol values during the 4 weeks of the study

Analysing the average triglycerides values during the 4 weeks of evaluation, it was concluded that there are no statistically significant differences between the treated and non-treated group (Figure 28).

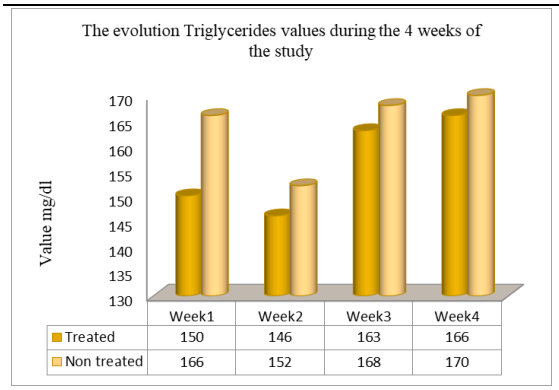


Figure 28.
Evolution of triglycerides values during the 4 weeks of the study

IBS is a digestive disease, which occurs in more than 10 % of the population [17], with a higher incidence in women [3, 33]. Patients diagnosed with IBS present themselves to the doctor, for abdominal pain, more frequently than the rest of the population, and they have a much lower quality of life, which can reduce their work ability [4, 42].

This was an efficacy and safety observational retrospective study performed in patients with IBS, treated with Drotaverine 80 mg tablets (Antispasmin® Forte 80 mg Biofarm, Romania) given 1 tablet three times daily for 2 weeks.

Therapy available for IBS treatment includes 5-HT agonists and antagonists, antispasmodics, prokinetics, bulking agents, and antidepressants [19, 33]. Some clinical trials were conducted to evaluate various treatment used in IBS, but until now, only muscle relaxants were shown to decrease abdominal pain [27, 43].

The majority of clinical trials evaluating the efficacy of antispasmodics were conducted 25-30 years ago, with only few trials conducted in the last decade [2, 29, 44-47].

Several studies addressing drotaverine efficacy are available in the literature [45, 48], but the insufficient number of randomized controlled trials for many of these therapies has limited the progress in the treatment of this disease [18, 24, 29, 30, 49, 50].

Drotaverine belongs to the musculotropic antispasmodic drugs. It is indicated in IBS because it relaxes the gastro-intestinal muscles, thus removing abdominal pain and improving intestinal transit.

Structurally, drotaverine hydrochloride is an isoquinoline derivative as well as papaverine. The spasmolytic effect is based on its action to inhibit the enzymatic activity of phosphodiesterase IV (PDE IV). As a result, cAMP concentration increases, which, by inactivating myosin light kinase (MLCK), leads to smooth muscle relaxation. Drotaverine has been shown to inhibit PDE IV *in vitro*, without inhibiting PDE III and PDE V isozymes.

From a functional point of view, PDE IV appears to be important in decreasing the contractile activity of smooth muscle, suggesting that selective inhibition of this isoenzyme may be useful in the treatment of gastrointestinal disorders caused by hypermotility and other conditions associated with spasm in the gastrointestinal tract [12, 44, 51, 52].

Drotaverine hydrochloride is effective in combating smooth muscle spasms of both nervous and muscular origin. Regardless of the autonomic innervation, drotaverine hydrochloride acts on the smooth muscles of the gastrointestinal and urogenital tracts, the biliary tract and the circulatory system [10, 27, 52-54].

The enzyme that hydrolyses cAMP from the myocardium and vascular smooth muscle cells is mainly represented by the PDE III isoenzyme. Since this enzyme is not inhibited by drotaverine hydrochloride, the drug does not cause important cardiovascular effects.

Due to its vasodilator effect, drotaverine hydrochloride improves tissue circulation. The effect of drotaverine is more intense than that of papaverine, its absorption is faster and more complete and the binding to plasma proteins is lower. Unlike papaverine, drotaverine does not cause adverse respiratory reactions.

Drotaverine hydrochloride is rapidly and completely absorbed after oral administration. It is highly bound to human plasma proteins (95-98%), especially to albumin, gamma and beta globulins. The maximum plasma concentration (Cmax) is reached 45 - 60 minutes after oral administration [13]. After metabolization, during the first hepatic passage, only 65% of the administered dose reaches the systemic circulation unchanged. Drotaverine is metabolized in the liver. Its plasma half-life is 8 - 10 hours. After 72 hours, drotaverine is no longer found in the body. It is eliminated through urine in proportion of more than 50% and in proportion of approximately 30% through faeces. It is excreted mainly in the form of metabolites, its unchanged form not being found in the urine.

Misra *et al*. [50] found that drotaverine decreased pain frequency and severity in 31.4%/71.4% of IBS patients as compared with placebo at the end of 2nd and 4th weeks, respectively. In another study, Pap *et al*. [26] had shown the efficacy of drotaverine in IBS *vs*. placebo. The authors found that the decrease of pain was 47% in the IBS treated group vs. 3% in the placebo group. The results of the present study were found to be in accordance with all the reported findings after 2 weeks and 4 weeks of treatment.

The improvement in abdominal pain observed in the group treated with drotaverine is due to the antispasmodic effect of drotaverine, by relaxing the intestinal smooth muscle by the inhibition of phosphodiesterase and by inhibition of Ca^{2+} release [2, 20].

This drotaverine effect could explain also the improvement of the intestinal transit, decreasing the

functional obstruction caused by increased phasic colonic contractions that may be present in constipation [30]. The management of IBS is more complex and includes an adequate pharmacological treatment, patient education as well, a specific diet and a good patient-physician relationship.

Another stage of the study concerned the global evaluation of the improvement of abdominal pain as it was perceived by the patient and rated by the clinician. In this case, VAS scale assessment was conducted at the beginning of the 3rd week and at the end of the evaluation period. 50 patients from the treated group perceived an improvement in pain in the third week of the study. At the end of the fourth week, 80 patients perceived this improvement. Our results are in accordance with the results published by Ramesh *et al*. [29], which show that there was also a statistically significant ($p < 0.01$) for the global relief in abdominal pain as perceived by the patient (85.9% *vs*. 39.5%) and rated by the clinician (82.4% *vs*. 36.5%) in the drotaverine group as compared with placebo group.

The second record of the improvement of pain severity score was done after the 4th week of evaluation. Even if the patients received the treatment only for 14 days, at the end of the 4 weeks of observation, the pain severity score was maintained in the same decreasing direction. There are other studies in the literature such as Ramesh *et al*. study [29], and Xue *et al*. [55] which suggest that the pain severity scores also decreased significantly in the drotaverine group as compared with untreated group at the end of the 4 weeks of the study. The pain frequency relief was also evaluated, and the results were similar to the ones obtained in 2014 by Ramesh *et al*. [30]. In their study the authors stated that pain frequency decreased significantly ($p < 0.01$) in 22 (25.9%), 51 (60%), and 66 (77.7%) patients in the drotaverine group, at the end of 2nd, 3rd, and at the beginning of the 4th week, respectively, as compared with 7 (9.4%), 16 (21.2%), and 23 (30.6%) in the untreated group. In his study, Ramesh [29], sustained also the role of a multidimensional therapeutic approach in the management of IBS and the evidence to support the use of drotaverine for abdominal pain.

While the statistical significance of the results is clear, the clinical significance is also notable, especially regarding pain reduction, colic episode frequency, and transit normalization. The reduction from 8 to 1 colic episode per day, alongside a 5-point pain score improvement, represents a substantial impact on patient comfort and daily functioning. Notably, patients with IBS-M experienced the most pronounced transit normalization, supporting drotaverine clinical relevance in this challenging subgroup.

These results are aligned with the previous results published by other authors like Misra *et al*. [50], Ramesh *et al*. [30], and Pap *et al*. [27], Al Ghamdi *et al*. [47] and Qin *et al*. [46].

Given that drotaverine is a phosphodiesterase inhibitor with effects on smooth muscles and the nervous system, its role in modulating gut function and neurochemical pathways may be particularly relevant in conditions where neuroinflammation plays a multiple role in pathogenesis, contributing at the same time to the generation of mood disorders, such as aluminium-induced depression [5648]. At the same time, drotaverine can also interfere with other neurotransmitters that act on muscarinic or cannabinoid receptors, or on calcium channels [57]. There are already data supporting the efficacy and safety of drotaverine as analgesic in renal colic [1].

Further investigation into drotaverine pharmacological effects could provide valuable insights into novel therapeutic approaches for enteric nervous system dysfunctions and their broader implications in gut-brain axis disorders.

This study has several limitations: sample size, lack of randomization, missing data from patients' charts, different abdominal pain location. In addition, early treatment termination was a limitation of the study. The study initially included 609 patients, but only 200 patients fulfilled in the inclusion criteria. Further studies are needed to confirm and compete these results.

Conclusions

In conclusion, the results of the present study showed that drotaverine improved abdominal pain in patients with irritable bowel syndrome. It was also effective in improving intestinal transit changes and all the specific symptoms of IBS. Regarding the safety of this treatment, 5 patients reported mild adverse events (flatulence, bloating, constipation, sleep disturbance, dizziness) after 10 treatment days. All these adverse events had a short duration and did not require discontinuation of therapy. Drotaverine did not affect the laboratory parameters analysed. It is thus concluded that Drotaverine (Antispasmin® 80 mg tablets Biofarm, Romania) has a positive benefit-risk ratio in patients with colic pain due to IBS. All these results support the use of drotaverine as a safe and effective treatment of abdominal pain in patients with IBS.

Acknowledgement

This work was financially supported by Biofarm S.A., Romania.

Conflict of interest

The authors declare no conflict of interest.

References

1. Dash A, Maiti R, Akantappa Bandakkanavar TK, Arora P, Intramuscular drotaverine and diclofenac in acute renal colic: a comparative study of analgesic efficacy and safety. *Pain Med*., 2012; 13(3): 466-471.
2. Annahazi A, Roka R, Role of antispasmodics in the treatment of irritable bowel syndrome. *World J Gastroenterol*., 2014; 20: 6031-6043.
3. Drossman DA, Camilleri M, Mayer EA, Whitehead WE, AGA technical review on irritable bowel syndrome. *Gastroenterology*, 2002; 123: 2108-2131.
4. Ford AC, Moayeddi P, American College of gastroenterology monograph on management of Irritable Bowel Syndrome. *Am J Gastroenterolol*., 2018; 113: 1-18.
5. Williams RE, Black CI, Determinants of healthcare-seeking behaviour among subjects with irritable bowel syndrome. *Aliment Pharmacol Ther*., 2006; 23: 1667-1675.
6. Na Y, Zhao J, Su Z, Jiao Y, The therapeutic effect of Changyuning Granules combined with retention enema on alleviating the symptoms of ulcerative colitis. *Farmacia*, 2021; 69(4): 705-711.
7. Pareek A, Chandurkar NB, Patil RT, Agrawal SN, Uday RB, Tambe SG, Efficacy and safety of aceclofenac and drotaverine fixed-dose combination in the treatment of primary dysmenorrhea: a double-blind, double-dummy, randomized comparative study with aceclofenac. *Eur J Obstet Gynecol Reprod Biol*., 2010; 152: 86-90.
8. Bolaji OO, Onyeji CO, Ogunaini AO, Olugbade TA, Ogunbona F, Pharmacokinetics and bioavailability of drotaverine in humans. *Eur J Drug Metab Pharmacokinet.*, 1996; 21(3): 217-221.
9. Dawood MY, Dysmenorrhea. *J Reprod Med.*, 1985; 30: 154-167.
10. Romics I, Molnar DL, Timberg G, et al., The effect of drotaverine hydrochloride in acute colicky pain caused by renal and ureteric stones. *BJU Int.*, 2003; 92: 92-96.
11. Drossman DA, Functional gastrointestinal disorders: History, pathophysiology, clinical features and Rome IV. *Gastroenterology*, 2016; 150(6): 1262-1279.
12. Blasko G, Pharmacology, mechanism of action and clinical significance of a convenient antispasmodic agent: Drotaverine. *J Am Med Assoc Ind Physicians'Update.*, 1998; 1: 63-69.
13. Ruigomez A, Wallander MA, Johansson S, Garcia Rodriguez LA, One-year follow-up of newly diagnosed irritable bowel syndrome patients. *Aliment Pharmacol Ther*., 1999; 13: 1097-1102.
14. Chan WY, Fuchs F, Powell AM, Effects of naproxen sodium on menstrual prostaglandins and primary dysmenorrhea. *Obstet Gynecol.*, 1983; 61: 285-291.
15. Snape WJ Jr., Role of colonic motility in guiding therapy in patients with constipation. *Dig Dis.*, 1997; 15: 104-111.
16. Darvish-Damavandi M, Nikfar S, A systematic review of efficacy and tolerability of mebeverine in irritable bowel syndrome. *World J Gastroenterol.*, 2010; 16: 547-553.
17. Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, editors, Rome II: The functional gastrointestinal disorders: Diagnosis, pathophysiology and treatment: A multinational consensus. *Degnon Associates*., 2000; 2nd ed.
18. Drossman DA, Thompson WG, The irritable bowel syndrome: Review and a graduated multicomponent treatment approach. *Ann Intern Med*., 1992; 116: 1009-1017.
19. Ghoshal UC, Abraham P, Bhatt C, Choudhuri G, Bhatia SJ, Shenoy KT, Banka NH, Bose K, Bohidar NP, Chakravartty K, Shekhar NC, Desai N, Dutta U, Das G, Dutta S, Dixit VK, Goswami BD, Jain RK, Jain S, Jayanthi V, Kochhar R, Kumar A, Makharia G, Mukewar SV, Mohan Prasad VG, Mohanty A, Mohan AT, Sathyaprakash BS, Prabhakar B, Philip M, Veerraju EP, Ray G, Rai RR, Seth AK, Sachdeva A, Singh SP, Sood A, Thomas V, Tiwari S, Tandan M, Upadhyay R, Vij JC, Epidemiological and clinical profile of irritable bowel syndrome in India: report of the Indian Society of Gastroenterology Task Force. *Indian J Gastroenterol.*, 2008; 27: 22-28.
20. Holdgate A, Oh CM, Is there a role for antimuscarinics in renal colic? A randomized controlled trial. *J Urol.*, 2005; 174(2): 572-575.
21. Colomier E, Algera J, Melchior C, Pharmacological therapies and their clinical targets in irritable bowel syndrome with diarrhea. *Front Pharmacol.*, 2021; 11: 629026.
22. Cangemi DJ, Lacy BE, Management of irritable bowel syndrome with diarrhea: a review of nonpharmacological and pharmacological interventions. *Therap Adv Gastroenterol.*, 2019; 12: 1756284819878950.
23. John T, James P, Linda L, John LR, Michael P, Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*, 2001; 94: 149-158.
24. Klein KB, Controlled treatment trials in the irritable bowel syndrome: A critique. *Gastroenterology*, 1988; 95: 232-241.
25. Radu N, Ghita I, Rau I, Therapeutic Effect of Polysaccharides from Plantago Species. *Mol Cryst Liq Cryst.*, 2010; 523(1): 236/808-246/818.
26. Pap A, Topa L, Balgha V, Kovats-Megyesi A, Pozsar J, Szikszai E, Drotaverine antagonizes spasm of Oddi's sphincter provoked by morphine in man. *Gastroenterology*, 1997; 112: A519.
27. Pap A, Hamvas J, Filiczky I, Burai M, Szikszay E, Beneficial effect of drotaverine in irritable bowel syndrome (IBS). *Gastroenterology*, 1998; 114: A818.
28. Gavrila R, Isaila M, Mircioiu C, Gherghiceanu F, Ghita I, Prasacu I, Mircioiu I, Biostatistic, legislativ and ethical problems of comparative clinical studies. I. Generic and biosimilar drugs case. *Farmacia*, 2018; 6: 930-937.
29. Ramesh RR, Nijhawan S, Comparative evaluation of efficacy and safety of drotaverine versus mebeverine in irritable bowel syndrome: a randomized double-blind controlled study. *Saudi J Gastroenterol.*, 2021; 27(3): 136-143.
30. Ramesh RR, Dwivedi M, Kumar N, Efficacy and Safety of Drotaverine Hydrochloride in Irritable Bowel Syndrome: A Randomized Double-Blind Placebo Controlled Study. *Saudi J Gastroenterol.*, 2014; 20(6): 378-382.

31. Rey E, Talley NJ, Irritable bowel syndrome: Novel views on the epidemiology and potential risk factors. *Dig Liver Dis.*, 2009; 41: 772-780.
32. Taher A, Schulz-Knappe P, Meyer M, Truss M, Forssmann WG, Stief CG, Jonas U, Characterization of cyclic nucleotide phosphodiesterase isoenzymes in the human ureter and their functional role in vitro. *World J Urol.*, 1994; 12(5): 286-291.
33. Papale AJ, Flattau R, Vithlani N, Mahajan D, Nadella S, A Review of Pharmacologic and Non-Pharmacologic Therapies in the Management of Irritable Bowel Syndrome: Current Recommendations and Evidence. *J Clin Med.*, 2024; 13(22): 6948.
34. European Medicine Agency, Guideline on de evaluation of medicinal products for the treatment of irritable bowel syndrome, 2014, Available from: https://www.ema.europa.eu.
35. Jensen MP, Chen C, Brugger AM, Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. *The Journal of Pain*, 2003; 4(7): 407-414.
36. Hawker GA, Mian S, Kendzerska T, French M, Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)*, 2011; 63: S240-S252.
37. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J; IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*, 2005; 113(1): 9-19.
38. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole ML, Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*, 2001; 94(2): 149-158.
39. Schmulson MJ, Drossman DA, What is new in Rome IV. *J Neurogastroenterol Motil.*, 2017; 23(2): 151-163.
40. Guyatt GH, Townsend M, Berman LB, Keller JL, A comparison of Likert and visual analogue scales for measuring change in function. *Journal of Chronic Disease*, 1987; 40(12): 1129-1133.
41. Hill P, Chronic pain: a consequence of dysregulated protective action. *Br J Pain*, 2019, 13(1): 13-21.
42. Camilleri M, Diagnosis and treatment of irritable bowel syndrome: A review. *JAMA*, 2021; 325(9): 865-877.
43. Liang J, Xiang C, Sun K, Bevacizumab in and first-line chemotherapy in the treatment of metastatic colorectal cancer: evaluation of clinical efficacy and progression-free survival. *Farmacia*, 2023; 71(4): 747-754.
44. Lehrer JK, Lichtenstein GR, Irritable Bowel Syndrome. Available from: www.emedicine.medscape.com.
45. Black CJ, Yuan Y, Selinger CP, Camilleri M, Quigley EMM, Moayyedi P, Ford AC, Efficacy of soluble fibre, antispasmodic drugs, and gut-brain neuromodulators in irritable bowel syndrome: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol.*, 2020; 5(2): 117-131.
46. Qin D, Tao QF, Huang SH, Chen M, Zheng H, Eluxadoline Versus Antispasmodics in the Treatment of Irritable Bowel Syndrome: An Adjusted Indirect Treatment Comparison Meta-analysis. *Front Pharmacol.*, 2022; 13: 757969.
47. Al Ghamdi K, Albluwi N, Alammari A, Alibrahim H, Al-Thabet A, Radhi J, Alnamshah F, Alghamdi K, Alshammari N, Ghalib S, Al Dawood A, The Efficacy and Safety of Antispasmodic agents in the Management of Irritable Bowel Syndrome: A Systematic Review. *J Healthc Sci.*, 2023; 3(6): 167-180.
48. Eder P, Kowalski P, Mastalerz-Migas A, Skrzydlo-Radomanska B, Cichy W, Proga K, Self-Medication with Drotaverine among Patients with Common Abdominal Symptoms and Treatment Efficacy from the Perspectives of Patients and General Practitioners-An Observational, Retrospective, Cross-Sectional Study Using Real-World Data. *J Clin Med.*, 2022; 11(11): 3156.
49. Jailwala J, Imperiale TF, Kroenke K, Pharmacologic treatment of the irritable bowel syndrome: A systematic review of randomized, controlled trials. *Ann Intern Med.*, 2000; 133: 136-147.
50. Misra SC, Pande R, Efficacy of drotaverine in irritable bowel syndrome: A double blind randomized, placebo controlled clinical trial. *Am J Gastroenterol.*, 2000; 95: 2544-2551.
51. Labrecque M, Dostaler LP, Rousselle R, Nguyen T, Poirier S, Efficacy of nonsteroidal anti-inflammatory drugs in the treatment of acute renal colic. A meta-analysis. *Arch Intern Med.*, 1994; 154: 1381-1387.
52. Lesbros-Pantoflickova D, Michetti P, Fried M, Beglinger C, Blum AL, Meta-analysis: The treatment of irritable bowel syndrome. *Aliment Pharmacol Ther.*, 2004; 20: 1253-1269.
53. Mangel AW, Northcutt AR, Review article: The safety and efficacy of alosetron, a 5-HT3 receptor antagonist, in female irritable bowel syndrome patients. *Aliment Pharmacol Ther.*, 1999; 13: 77-82.
54. Chirila M, Ghita I, Fulga I, Current knowledge on bupropion and varenicline clinical efficacy in nicotine. *Farmacia*, 2015; 63(1): 1-7.
55. Xue Xing-cun MB, Qi Xiao-Xia MB, Wan Xiao-Yan MM, Randomized controlled study of efficacy and safety of drotaverine hydrochloride in patients with irritable bowel syndrome. *Medicine*, 2017; 96(51): e9235.
56. Handra CM, Ghita I, Ulmeanu A, Enache AM, Epureanu F, Coman O A, Fulga I, Depressive clinical manifestations associated with professional aluminum exposure. *Rev Chim.*, 2019; 70(6): 2162-2167.
57. Segarceanu A, Ghita I, Sova AC, Radu MC, Fulga I, Antinociceptive properties of diethylamine in rodents: role of the cannabinoid and opioid receptors. *Farmacia*, 2014; 62(3): 589-600.