Symptomatic Pain Management in Irritable Bowel Syndrome

Reviewed by:

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Irritable Bowel Syndrome: Overview

Functional bowel disorders comprise a spectrum of chronic gastrointestinal (GI) disorders characterized by abdominal pain, bloating, distention, and/or bowel habit abnormalities (constipation, diarrhea, or mixed constipation and diarrhea) in the absence of any organic or biochemical pathology.[1,2] These are primarily attributed to the deranged functioning of the well-coordinated brain-gut axis that results in an array of symptoms that can affect any part of GI tract.[3] Irritable bowel syndrome (IBS) is a highly prevalent functional bowel disorder characterized by symptoms of abdominal pain or discomfort that occur with changes in bowel function.[4-6]

Clinical Manifestations of IBS

IBS displays a wide range of symptoms of gastrointestinal dysmotility and visceral hypersensitivity.[7] Abdominal pain and altered bowel habits are the cardinal symptoms of IBS. Besides, it also exhibits extraintestinal symptoms.[8,9] Table 1 illustrates the gastrointestinal and extraintestinal symptoms of IBS. The intensity and frequency of these symptoms usually vary among patients. This variation in clinical presentation, together with the fact that many patients with IBS do not seek medical opinion, suggests that patients with symptoms related to IBS should be approached with a high level of clinical suspicion.[10]

Global Burden of IBS

IBS is among the most prevalent adult functional gastrointestinal disorders (FGIDs) worldwide.[8] Although regional variation exists, it has been estimated that IBS affects 5% to 20% of the worldwide population.[10] The prevalence of IBS is most common between 20 and 40 years of age with a significant female predominance (3:1). Conventionally, IBS has been known to impose considerable health burden in the Western countries; however, its prevalence appears to be increasing in Asian countries, which is a cause of concern. Studies have reported the prevalence of IBS ranging from 3.7% to 22% in Asian population, with some studies reporting the prevalence to be as much as 24%.[9,11]

Table 1: Clinical presentation of irritable bowel syndrome

Gastrointestinal symptoms
• Chronic abdominal pain with variable intensity and periodic exacerbations
• Altered bowel habits ranging from diarrhea, constipation, alternating diarrhea and constipation, or normal bowel habits alternating with either diarrhea and/or constipation
• Diarrhea characterized by frequent loose stools of small to moderate volume
• Prolonged constipation with interludes of diarrhea or normal bowel function with often hard, pellet-shaped stools and a sense of incomplete evacuation even when the rectum is empty
Extraintestinal symptoms
• Impaired sexual function
• Dysmenorrhea
• Dyspareunia
• Increased urinary frequency and urgency
• Fibromyalgia symptoms

Prevalence of IBS in India

Past epidemiological studies lacked substantial data on IBS prevalence in Indian subcontinent. However, an upsurge in the prevalence of IBS over the last few years compelled Indian investigators to focus on this issue. This led to the availability of few Indian studies that provided information

on the prevalence of IBS and its profile among Indian patients. According to the symptom presentation, the prevalence of IBS in India has been found to be 4.2%.[12,13] The Task Force of the Indian Society of Gastroenterology (ISG)[13] attempted to investigate the profile of IBS in the Indian population. The characteristic findings of the study were as follows:

- IBS was predominantly present in men unlikely to the female predominance in the Western population
- Another important finding was; abdominal pain or discomfort being an essential symptom of IBS, not universally present in all Indian patients with IBS.

Another Indian study,[14] done in a rural community in Northern India, found the prevalence of IBS to be 4%. In contrast to the previous study (performed by the Task Force of the ISG), this analysis reported more IBS occurrence in women, similar to that seen in the Western data. This study[14] also showed diarrhea-predominant IBS (1.5%) to be more common than constipation-predominant IBS (0.3%) in Indian patients. The findings procured from the above study were consistent with Ghoshal et al's[13] earlier observation that Indians were more likely to have higher frequency of bowel movements than their Western counterparts.

Impact on the Quality of Life

Symptoms of IBS are chronic and recurrent, and they wax and wane in severity with time. These symptoms are frequently bothersome and substantially impact the daily activities of the patients. Therefore, IBS portends to considerable impairment in quality of life and loss of work productivity. In fact, health-related quality of life in IBS is more adversely affected than in other chronic disorders, such as gastroesophageal reflux disease (GERD) and diabetes.[15] These patients often report deterioration in physical functioning, mental health and general health perception.[2] Many past studies have evaluated the effect of IBS on work and quality of life and have shown deterioration in quality of life and increased loss of productive work due to IBS. The need to diagnose this disease early and institute appropriate management should be emphasized in light of evidence demonstrating improvement in quality of life with treatment of IBS.[16]

Diagnosis of IBS

IBS is essentially a clinical diagnosis that can be made by performing a careful review of the patient's symptoms, taking a detailed history (diet, medication, medical, surgical, and psychological history), evaluating the patient for the presence of warning signs, performing a guided physical examination, and using the Rome IV criteria. In most cases with typical symptoms, detailed diagnostic investigations, including colonoscopy, are generally not required to make a diagnosis, especially if there are no "red flag" signs (patients aged >50 years; unintentional weight loss; nocturnal symptoms; symptoms of short duration; hematochezia, anemia or a family history of colorectal cancer or inflammatory bowel disease).[8,10]

Since many patients with suspected IBS symptoms present in primary care practice, it is prudent to identify diagnostic tests which may be appropriate in select cases. Often, these tests mainly aim to rule out other differential diagnosis of IBS, and include: full blood count; erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); tissue transglutaminase/endomysial antibody (celiac disease serology); thyroid function tests (TFTs); and stool test for parasites. However, use of ultrasound, colonoscopy, and TFTs in the diagnosis and management of IBS in patients meeting the diagnostic criteria remains ambiguous.[17,18]

The New ROME IV Diagnostic Criteria for IBS

The new ROME IV has introduced certain changes in the ROME III criteria. The ROME III criteria used to characterize IBS on the basis of abdominal pain or discomfort associated with defecation or changes in bowel habit, and with features of disordered defecation. However, the new ROME IV now requires that patients have abdominal pain and the term discomfort is now eliminated (Table 2).[8,19-21]

Based on stool consistency, the Rome IV criteria classify IBS into constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), IBS alternating between constipation and diarrhea (IBS-M), or unclassified IBS (Box 1).[19,20]

Pain in IBS: A Major Challenge

In patients with IBS, abdominal pain is considered the most bothersome symptom and also the most common reasons of seeking medical care. Recurrent abdominal

Table 2: Changes in diagnostic criteria in Rome III and Rome IV

Rome III	ROME IV
Recurrent abdominal pain or discomfort (defined as an uncomfortable sensation not described as pain) for at least three days/month in the last three months, associated with two or more of the following: • Improvement with defecation • Onset associated with a change in the frequency of stool • Onset associated with a change in the form (appearance) of stool	Recurrent abdominal pain on average at least one day per week in the last three months, associated with two or more of the following criteria: • Related to defecation • Associated with a change in the frequency of stool • Associated with a change in the form (appearance) of stool

pain is the central feature of pain-associated FGIDs such as IBS. In a report by the ISG Task Force, it has been shown that as much as 70% of patients with IBS have abdominal pain or discomfort that considerably affects the patient's quality of life. This functional association is particularly important in the setting where chronic abdominal pain is associated with abnormality in stool consistency and frequency. The underlying cause of abdominal pain in IBS has traditionally been ascribed to smooth muscle spasm, and it generally keeps recurring.[22-25]

Association Between Lactose Intolerance and IBS

IBS and lactose intolerance may present with similar symptoms and both conditions are common worldwide;

Box 1: Rome IV irritable bowel syndrome–subtypes criteria

- **IBS-C:** >25% of bowel movements with Bristol Stool Scale Types 1–2 (hard or lumpy stools) and <25% with Types 6–7 (loose or watery stools)
- **IBS-D:** >25% of bowel movements with Bristol Stool Scale Types 6–7 and <25% with Types 1–2
- **IBS-M:** >25% of bowel movements with Bristol Stool Scale Types 1–2 and >25% with Types 6–7
- **IBS-U:** Patients meet diagnostic criteria for IBS but their bowel habits (stool consistency) cannot be accurately categorized in any of the above subtypes

Abbreviations: IBS, irritable bowel syndrome; IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhea; IBS-M, IBS with mixed bowel habits; IBS-U, unclassified IBS.

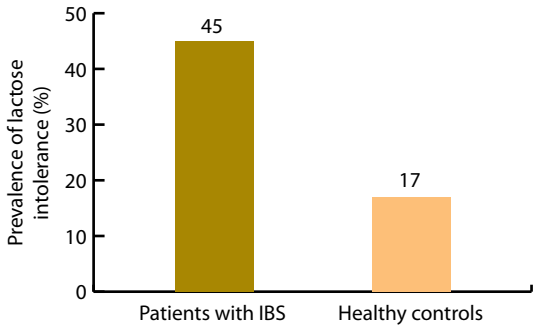
it is estimated that 4–78% patients with IBS in different geographic regions may have lactose intolerance. The hypothesis for this is that following ingestion of lactose, hydrogen gas is produced and gut distention is promoted due to bacterial fermentation of the unabsorbed lactose. The diagnosis of lactose malabsorption and intolerance in symptomatic patients with IBS can be confirmed by hydrogen breath test (HBT). In fact, lactose HBT offers an effective non-invasive method to detect excessive production of hydrogen as seen in lactose malabsorption and intolerance.[26-28]

Patients with IBS have been found to have considerably more subjective lactose intolerance complaints (abdominal pain, bloating, distention, flatulence, and diarrhea) as compared to those without IBS, and to have increased likelihood of lactose malabsorption than the general population.[27,29] An Asian study[29] aimed to investigate the prevalence of lactose intolerance in patients with IBS and asymptomatic healthy controls. A total of 109 eligible patients with IBS and 50 healthy controls were enrolled in this study. Lactose malabsorption (LM) was diagnosed by lactose HBT and was defined by peak breath H_2 excretion over the baseline level of ≥20 ppm. Lactose intolerance was defined in LM patients with positive symptoms during the observation time. The results revealed a higher prevalence of lactose intolerance in patients with IBS (45%) as compared to healthy controls (17%) (Figure 1).

Herein, the prevalence of lactose intolerance may however vary according to the type of IBS; with patients with IBS-D and indeterminate type of IBS having a higher incidence of lactose intolerance than those with IBS-C.[13,30] In an Indian study[26] that aimed to evaluate the frequency of lactose intolerance in patients with IBS and its various subtypes as compared with healthy subjects, it was observed that lactose intolerance as diagnosed either by lactose HBT or lactose tolerance test was 82% among patients with IBS as compared to 77% among the healthy controls. The frequency of lactose intolerance was 86% in IBS-D as compared to 80% in indeterminate IBS and 66% in IBS-C (Figure 2). Findings from these studies substantiate an increased risk of lactose intolerance in patients with IBS-D.[31,32]

Dietary modifications (lactose-reduced diet) are the mainstay of management in such cases with food

Figure 1: Prevalence of lactose intolerance in patients with irritable bowel syndrome and healthy controls

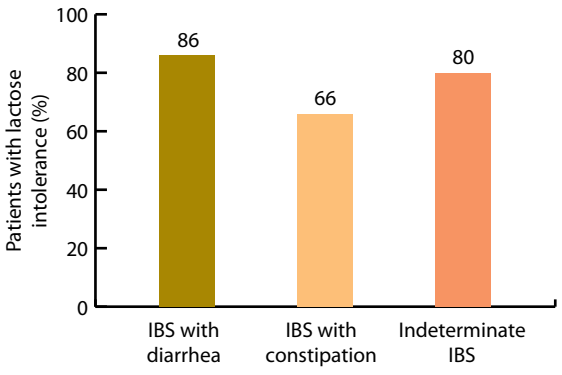


intolerance. Usually, IBS patients are advised to avoid milk and dairy products, which may further decrease the quality of life of patients and may also affect bone health in the long run; therefore, care should be taken with restrictive diets. Importantly, these IBS patients with lactose intolerance may benefit by exogenous supplementation of the lactase enzyme. In India, oral lactase enzymes are available which can be taken to digest milk and dairy products.[33-36]

Management of IBS with Predominant Pain Symptoms

Abdominal pain is one of the most commonly encountered and vexing symptoms of IBS, and it is considered among the most frequent reasons of seeking medical care.

Figure 2: Frequency of lactose intolerance in patients with various subtypes of IBS



This functional association is especially pertinent in the setting where chronic abdominal pain is associated with abnormality in stool consistency and frequency. The underlying cause of abdominal pain in IBS has been conventionally attributed to smooth muscle spasm, and it generally keeps recurring. Considering the role of smooth muscle spasm in the etiology of abdominal pain, it is reasonable to use antispasmodic drugs in patients with IBS. In fact, antispasmodic drugs have been and remain the mainstay of therapy and these agents have frequently demonstrated good symptom relief.[23,24,37]

Role of Antispasmodics in Abdominal Pain: Focus on Drotaverine

As smooth muscle contractions account for important symptoms of IBS, in particular abdominal pain, therefore, antispasmodic drugs have been used in patients with IBS, and have demonstrated symptom relief. Drotaverine is one such antispasmodic agent that is suited for oral administration, and it is capable of relieving or preventing smooth muscle spasm of various organs. In fact, it contributes very effectively in relieving painful spasms in a large variety of diseases, including those of gastroenterological origin. Drotaverine directly normalizes the dysmotility of intestinal tract by relaxing distal muscles and sphincters participating in peristaltic reflex. Essentially, Drotaverine would help in prolonging the pain-relief, and is efficacious for the maintenance of spasmolysis. Moreover, the drug is free of the side-effects associated with anti-cholinergic antispasmodics, such as hyoscyamine, dicyclomine, propantheline, and mebeverine, and may be given safely over long-term. Another significant advantage of drotaverine is that, unlike other conventional antispasmodics, it does not mask the symptoms of acute abdomen or interfere with diagnostic precision while providing optimum pain control. In humans, the drug exhibits quick absorption, with half-life of absorption 12 minutes after oral dosing, and reaching maximum plasma concentrations within 45 minutes of administration. In several studies, drotaverine has shown significant improvement in stool frequency, consistency, urgency, and flatulence. It also displays efficacy against spastic and motility disorders of the gastrointestinal smooth muscle as shown in multiple clinical studies.[37-42]

Evidence-Based Efficacy of Drotaverine

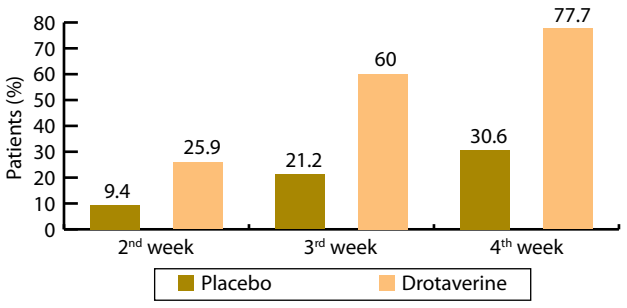
Xue XC et al[11] conducted a study to assess the efficacy and safety of drotaverine hydrochloride in patients with IBS. A total of 144 patients with IBS were included in the study and they were randomized into treatment group and placebo group in a 1:1 ratio. Patients were administered either drotaverine, or placebo 80-mg tablet, 3 times daily for a total of 4 weeks. It was observed that drotaverine can reduce the severity of pain evaluated by the visual analog scale (VAS) score ($p<0.01$), and can also decrease the stool frequency ($p<0.01$), as well as the Bristol score ($p<0.01$) compared with placebo at the end of the 4-week treatment (Table 3). In a nutshell, this study suggests that drotaverine is a promising therapeutic agent to alleviate symptoms of irritable bowel syndrome.

Rai and colleagues[37] evaluated the efficacy and tolerability of drotaverine hydrochloride (80 mg tablet, TID) in 180 patients with IBS, and observed a significant decrease in both the pain frequency and pain severity scores. The results revealed 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 4th week, respectively, as compared with 8 (9.4%), 18 (21.2%), and 26 (30.6%) in the placebo group (Figure 3). Pain severity scores also decreased significantly in the drotaverine group (77.7%) as compared to placebo (30.6%) after 4 weeks. There was a statistically significant ($p<0.01$) global relief in abdominal pain as perceived by the patient (85.9% vs 39.5%, respectively) and the clinician (82.4% vs 36.5%, respectively) in the drotaverine group as compared to placebo group. Moreover, drotaverine group was found to exhibit marked improvement in the stool frequency than the placebo group. The drug was well-tolerated without any substantial adverse effects. Therefore, this study suggested that treatment of abdominal symptoms

Table 3: Outcome measurements of total symptoms at the end of the 4 weeks treatment

Outcome measurements	Treatment group (n=72)	Placebo group (n=72)	*p*-value
Visual analog scale	1.8 ± 0.7	4.4 ± 1.5	< 0.01
Stool frequency	1.4 ± 0.6	2.9 ± 0.9	< 0.01
Bristol score	5.1 ± 0.6	5.6 ± 1.0	< 0.01

Figure 3: Patients experiencing reduction in pain frequency with drotaverine versus placebo



related to IBS with drotaverine HCl 80 mg given three times daily for 4 weeks is more effective than placebo.

In another double blind, randomized, placebo control study, conducted among 62 patients (mean age 50.8±14.2 years) with IBS and constipation, Pap and colleagues[40] demonstrated that 8 weeks of treatment with drotaverine (n=30) significantly reduced the abdominal pain by 47% while in the placebo group (n=32), severity of pain increased by 3% (Figure 4). The active treatment was deemed effective by 62.5% (15/24) of the patients and by 71% (17/24) of the physicians. This study suggested that drotaverine can effectively diminish abdominal pain and bloating in patients with IBS.

In a prospective double blind, randomized study conducted by Misra et al,[42] a total of 70 patients with IBS (aged between 18 and 60 years) were randomly prescribed either drotaverine (80 mg TID) or placebo over a 4-week treatment period followed by a 4-week follow-up phase. The results of the study revealed a decrease in pain frequency in 11 (31.4%) patients in the drotaverine group versus 2 (5.7%) in the placebo group after 2 weeks. After 4 weeks of therapy, 25 (71.4%) patients in the drotaverine group experienced reduction in pain frequency, compared to 11 (31.4%) patients in the placebo group (Figure 5). In addition, a decrease in pain severity scores was also noted, with 25 (71.4%) in the drotaverine group and only 11 (31.4%) with placebo at 4 weeks. When compared to placebo, drotaverine also showed global improvement in abdominal pain (74.2% vs. 37.1%) and stool frequency (25.7% vs. 2.8%) without any overall effect on the bowel

Figure 4: Change in abdominal pain severity from baseline with drotaverine versus placebo in patients with IBS

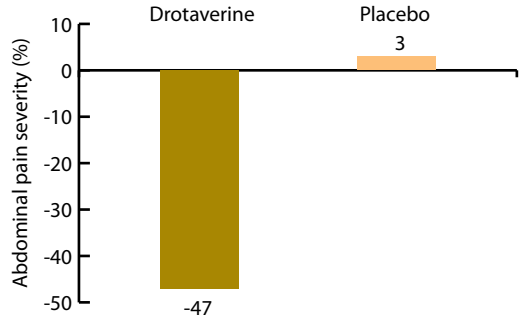
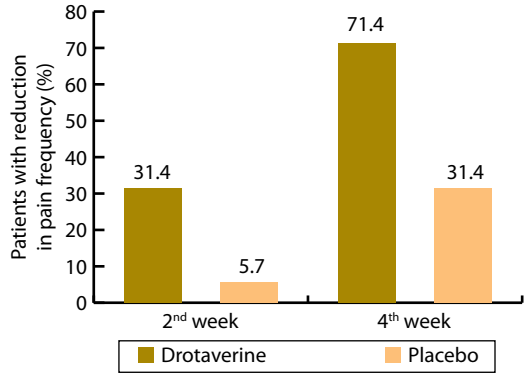


Figure 5: Reduction in pain frequency with drotaverine versus placebo in patients with IBS



movements. Therefore, this study demonstrated that drotaverine produces global improvement in abdominal pain in patients with IBS.

Sun J *et al*,[43] in a prospective, self-controlled, multi-center clinical trial, demonstrated that the average weekly score for abdominal pain in IBS patients was significantly decreased (0.66±0.59) in patients following drotaverine therapy as compared to those before treatment (1.42±0.42); the overall efficacy rate was 77.9% (Figure 6). There was a significant increase in the average daily stool frequency in IBS-C group (0.8±0.3 vs. 0.6±0.4), while a significant decrease was observed in IBS-D group (1.6±0.8 vs. 2.8±1.2). This study suggested that drotaverine can effectively improve the symptoms of IBS patients with abdominal pain, difficulty in passing stool and defecation effort. Also, varying degrees of improvement may be observed in bowel urgency and other symptoms. It is effective and well-tolerated in treating all subtypes of IBS.

The efficacy of drotaverine was further substantiated in a randomized control study, wherein Rai and Nijhawan[44] demonstrated that drotaverine was significantly more effective than mebeverine in alleviating pain severity, frequency and stools-related symptoms of IBS. A total of 200 patients with IBS were assigned to either of the two study groups.

- Group A (n=100): Drotaverine 80 mg – Three times a day, one hour before meals for 4 weeks
- Group B (n=100): Mebeverine 135 mg – Three times a day, one hour before meals for 4 weeks

The results demonstrated a fall in pain severity score from 6.02 to 4.8 on day 3 in Group A as compared to decrease from 6.72 to 6.62 in Group B ($p<0.01$). This significant reduction in pain severity score was observed till the end of the study; from 6.02 to 1.78 (70.4% reduction) in Group A versus 6.72 to 3.62 (46.1% reduction) in Group B ($p<0.05$) (Figure 7). Likewise, patients in Group A demonstrated a significant reduction in pain frequency and straining as compared to those in Group B. Also, change of 1 score in Bristol stool chart (BSC) was achieved by 55% of patients in Group A versus 30% in Group B. Proportion of patients achieving complete smooth bowel movement increased from 10% to 55% in Group A versus 8% to 25% in Group B. There was also a significant improvement in Patient's evaluation of Global Assessment of Symptoms ($p<0.05$) and Patient Assessment of Constipation - Quality Of Life

Figure 6: Pain scores before and after drotaverine therapy in patients with IBS

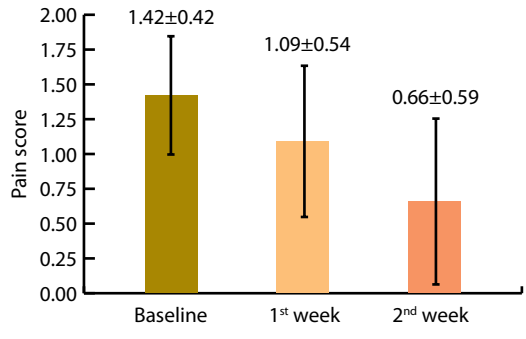
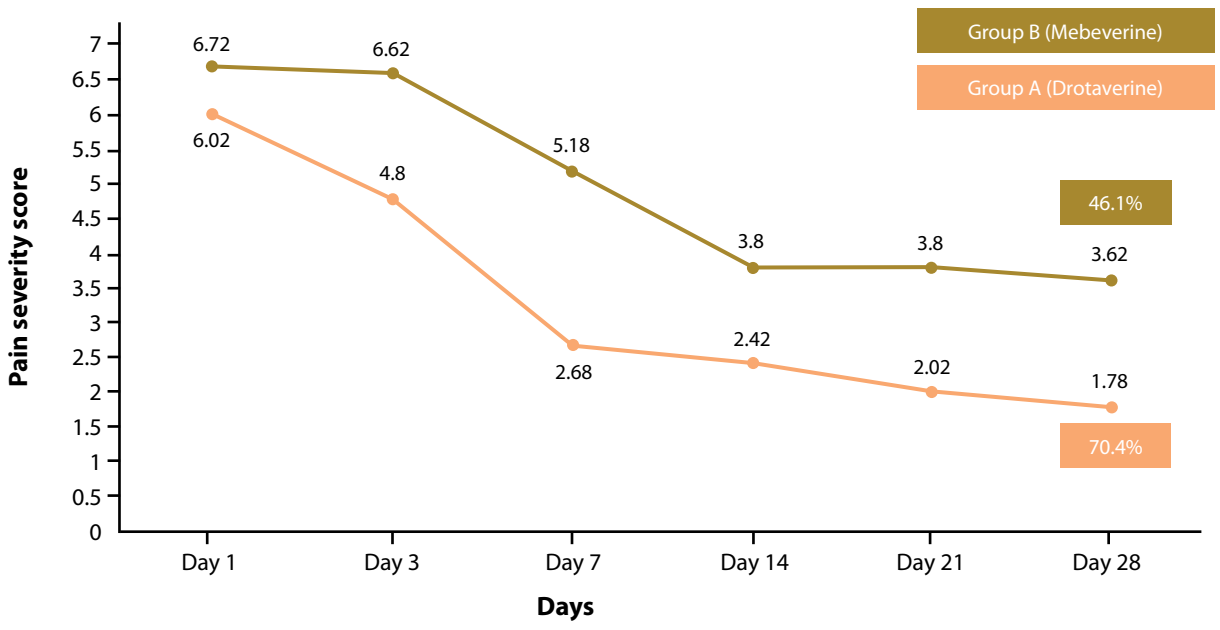


Figure 7: Change in Pain Severity Score in patients with IBS with drotaverine versus mebeverine therapy



(PAC-QOL) ($p<0.01$) in Group A compared to Group B. Thus, it could be substantiated that drotaverine was significantly superior in efficacy as compared to mebeverine in the symptomatic treatment of patients with IBS.

Conclusion

Irritable bowel syndrome is the most common functional gastrointestinal disorder characterized by abdominal pain or discomfort and alteration of bowel habits in the absence of an organic disorder. The underlying cause of abdominal pain in functional gastrointestinal disorders including IBS has been conventionally attributed to smooth muscle spasm. Considering the role of smooth muscle spasm in the etiology of abdominal pain, it is reasonable to use antispasmodic drugs in patients with IBS. In this context, drotaverine, a phosphodiesterase IV inhibitor that relaxes the gut smooth muscles, has been shown to exert a good relaxing effect on intestinal smooth muscle, resulting in pain alleviation in patients with functional gastrointestinal disorders. The drug exhibits quick absorption, and has a quick onset of action. Drotaverine directly normalizes the dysmotility of intestinal tract and provides global relief from abdominal pain in IBS. Furthermore, it is well-tolerated and is devoid of anticholinergic side-effects. In several studies, drotaverine has shown significant improvement in stool frequency, consistency, urgency, and flatulence. It also displays efficacy against spastic and motility disorders of the gastrointestinal smooth muscle as shown in multiple clinical studies. Lactose intolerance may also present symptoms similar to IBS. Individuals with IBS have significantly more subjective lactose intolerance than the healthy individuals, and the risk of lactose intolerance is increased in patients with diarrhea-predominant IBS. Dietary modifications are a mainstay of management in such cases; these IBS patients with lactose intolerance may benefit by exogenous supplementation of the lactase enzyme.

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