Role Of Drotaverine Hydrochloride In Irritable Bowel Syndrome

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Irritable bowel syndrome: An overview

Irritable bowel syndrome (IBS) is a highly prevalent functional gastrointestinal (GI) disorder, characterized by chronic GI symptoms including abdominal pain and altered bowel habits in the absence of any organic or biochemical pathology. Despite intense research done over the last few years on functional GI disorders, in particular IBS, their pathophysiology continues to be debatable. However, most experts argue for a multifactorial etiology of these disorders, with stress and visceral hypersensitivity playing prime roles in their development.[1-4]

In general, IBS is well recognized for its consortium of symptoms including abdominal pain and alterations in the pattern of defecation in term of stool consistency and/or frequency (Box 1). Although the condition is not life threatening; its symptoms are bothersome and painful. 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 identified early and treated appropriately.[5-8]

Box 1: Clinical presentation of irritable bowel syndrome

Gastrointestinal symptoms

- Abdominal pain and discomfort with variable intensity and periodic exacerbations
- Bloating
- Altered bowel habits
- Variation between periods of constipation and diarrhea

Extraintestinal symptoms

- Impaired sexual function
- Dysmenorrhea
- Dyspareunia
- Increased urinary frequency and urgency
- Fibromyalgia symptoms

Adapted from: El-Salhy M. Irritable bowel syndrome: diagnosis and pathogenesis. *World J Gastroenterol.* 2012;18(37):5151-63.

Burden of irritable bowel syndrome

World-wide prevalence

IBS is widely prevalent around the world and affects as many as 9-23% of individuals worldwide. It is seen more often in women than in men (3:1), and being more commonly diagnosed in patients between 20 and 40 years of age. Considerable regional variation in its prevalence has also been recorded. The disorder is particularly common among the Western population where its prevalence has been reported to be between 10-15%.[3,8] In the Asian population, studies have reported the prevalence of IBS ranging from 3.7% to 22%, with some studies reporting the prevalence to be as much as 24%.[9,10] Thus, although IBS has traditionally imposed significant health burden in the Western countries, its relentless rise in Asia has been a matter of concern that warrants prompt evaluation and implementation of corrective measures.

Prevalence in India

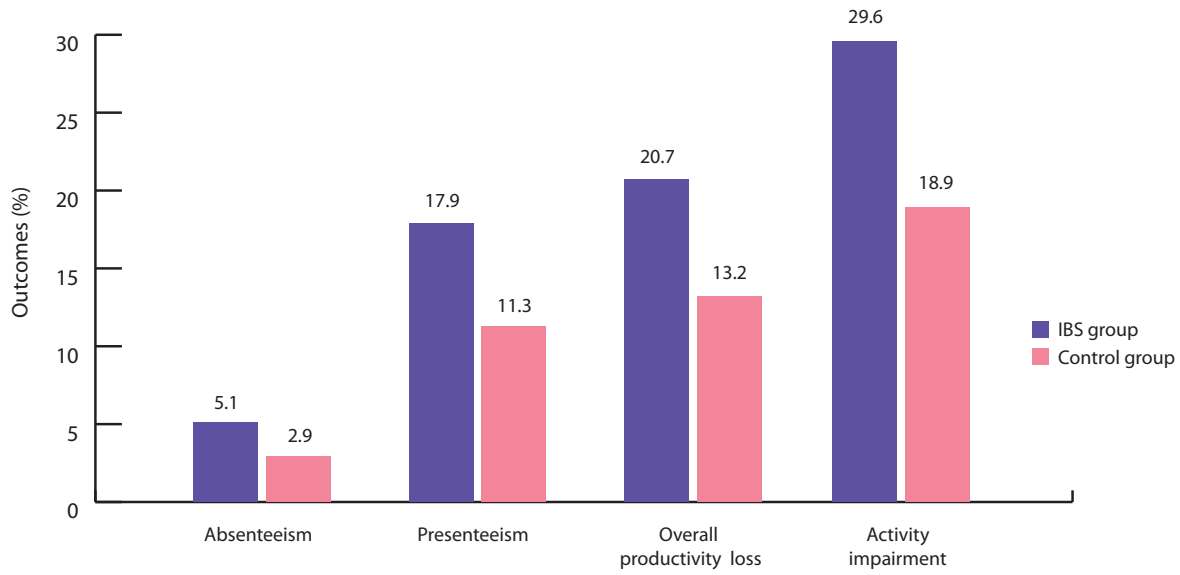
Past epidemiological studies lacked substantial data on IBS prevalence in the Indian subcontinent. However, an upsurge in the prevalence of IBS over the last few years compelled Indian investigators to focus on this issue. This led to the availability of few Indian studies that provided information on 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%.[11,12]

The Task Force of the Indian Society of Gastroenterology[12] attempted to investigate the profile of IBS in the Indian population, and observed that IBS was predominantly present in men, unlikely to the female predominance in the Western population. Another Indian study,[13] done in a rural community in Northern India, found the prevalence of IBS to be 4%. In contrast to the previous study[12], this analysis reported more IBS occurrence in women, similar to that seen in the Western data. This study also showed diarrhea-predominant IBS (1.5%) to be more common than constipation-predominant IBS (0.3%) in Indian patients. This suggests that Indian patients with IBS are more likely to have higher frequency of bowel movements than their Western counterparts.[13]

Impact of IBS on the quality of life

Symptoms of IBS are chronic, recurrent, and wax and wane in severity with time. These symptoms are frequently bothersome and considerably impact the daily activities of the patients. Therefore, IBS portends to considerable impairment in quality of life (QoL) and loss of work productivity.[14] Patients with IBS often

Figure 1: Effect of irritable bowel syndrome on work and quality of life



Adapted from: Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. *Health Qual Life Outcomes.* 2017;15:35.

report deterioration in physical functioning, mental health and general health perception.[1]

In a study[15] conducted among employed US population, IBS was associated with greater than 20% reduction in work productivity due to its associated GI symptoms; employees diagnosed with IBS had significantly lower scores on all domains of the SF-36v2 – a widely used questionnaire for measuring quality of life. Compared with controls, the IBS cohort reported significantly lower health-related QoL and greater absenteeism, presenteeism, overall work productivity loss, and activity impairment (Figure 1). 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]

Management approaches for irritable bowel syndrome

The treatment of IBS can be particularly demanding since symptoms often are recurrent and resistant to therapy. The primary goals of treatment are symptom relief and improved quality of life, rather than disease modification or cure. Essentially, the management starts with patient education and counseling on dietary and lifestyle modifications, and stress relief.[17,18]

Dietary intervention

Diet modification is one of the most frequently used interventions for patients with IBS. Increasing fiber intake has traditionally been considered one of the first-line treatment approaches advocated in patients with IBS. Soluble fibers are shown to improve symptoms of IBS; fiber's beneficial effects may reflect colonic fermentation with production of short-chain fatty acids or its action as a prebiotic.[9,19,20]

Pharmacological interventions

IBS presents as a complex of symptoms ranging from intestinal inflammation to psychological dysfunction. Therefore, it is important to address the predominant symptoms first. Existing drug therapies are administered based on a diagnosis of either diarrhea-predominant IBS (IBS-D) or constipation-predominant IBS (IBS-C). As follows, in patients presenting with IBS-D, antidiarrheals (such as loperamide) can be used; whereas in those with IBS-C, use of laxatives (such as polyethylene glycol) and bulking agents may be used to ameliorate the symptoms.[9,17]

Management of IBS with predominant pain symptoms

Abdominal pain is one of the most commonly encountered and vexing symptoms of IBS.[21] Considering the role of smooth muscle spasm in the etiology of abdominal pain, it is reasonable to use antispasmodic drugs in patients with IBS.[22] An appraisal of studies[23] evaluating symptom effects with antispasmodics in patients with IBS revealed relief of abdominal pain in 58% of patients compared to 46% receiving placebo. Hence, it is worth considering use of these agents in IBS, particularly when abdominal pain and diarrhea are the predominant symptoms.[21]

Antispasmodic drugs, such as the anti-muscarinics (dicyclomine and hyoscamine) are widely used in the treatment of spasmodic pain in IBS; however, in clinical experience, the individual response to this therapy is variable and unimpressive. In addition, anticholinergic side-effects like dry mouth, urinary retention,

and constipation further support their limited prescription for management of gastrointestinal symptoms.[24,25] It is therefore rational to use antispasmodic agents other than anticholinergics, particularly in IBS-C. In this context, Drotaverine, a directly-acting smooth muscle antispasmodic agent, seems a reasonable choice, since it does not have anticholinergic side effects.[22,26]

Role of antispasmodics in abdominal pain: Focus on Drotaverine

Drotaverine is an antispasmodic agent that has been shown to exert a good relaxing effect on intestinal smooth muscle, resulting in pain alleviation. Importantly, Drotaverine does not have side effects similar to anticholinergics.[22,26] Additionally, it is also shown to normalize the GI motility; therefore, it may be an effective option for patients with IBS-C as well as those with IBS-D. 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 (Box 2). 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.[27]

Box 2: Benefits of Drotaverine

- Site specific - phosphodiesterase IV inhibitor
- Rapid onset of action – provides rapid pain relief in just 5-12 min
- Does not mask the diagnosis of the pathological condition and provides instant relief
- Can be administered to relieve pain symptomatically, before any definitive therapy is instituted
- Does not compromise the management of underlying organic disorders
- Does not induce anticholinergic side effects as seen with other anticholinergic antispasmodics
- Normalizes the gastrointestinal motility
- Lacks anticholinergic side effects, such as dryness of mouth and constipation; hence, it can be prescribed in both types of IBS (constipation-predominant IBS and diarrhea-predominant IBS)
- Limited drug-drug interactions

Adapted from: Blasko G. Pharmacology, mechanism of action and clinical significance of a convenient antispasmodic agent. *JAMA India.* 2001;4(12):55-6.

Drotaverine is a selective inhibitor for phosphodiesterase IV, an enzyme responsible for breakdown and inactivation of cAMP and cGMP, which regulates the contractile activity of smooth muscles. Besides, it also exhibits a mild Ca-channel blocking effect. Thus, Drotaverine displays efficacy against spastic and motility disorders of the gastrointestinal smooth muscle and provides relief in abdominal spasms as shown in various clinical studies.[27-30]

Evidence based efficacy of Drotaverine

A recent study by Xue XC *et al*[10] demonstrated that Drotaverine is a promising therapeutic agent to alleviate symptoms of IBS. In this study, a total of 144 patients with IBS 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) scale ($p < 0.01$), and 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 1). No serious and remarkable differences in adverse events were found in and between both groups.

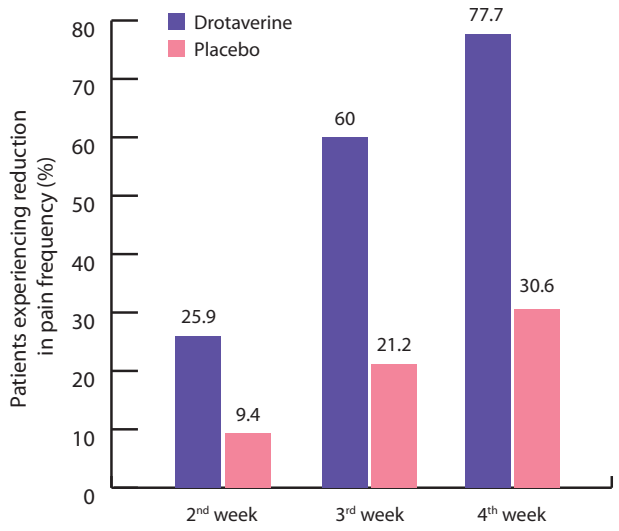
Table 1: Outcome measurements of total symptoms at the end of 4 weeks in the treatment (Drotaverine) versus placebo group

Outcome measurements	Treatment group (n=72)	Placebo group (n=72)	p
Visual analog scale	1.8 ± 0.7	4.4 ± 1.5	<.01
Stool frequency	1.4 ± 0.6	2.9 ± 0.9	<.01
Bristol score	5.1 ± 0.6	5.6 ± 1.0	<.01

Adapted from: Xue X, Qi XX, Wan XY. Randomized controlled study of efficacy and safety of drotaverine hydrochloride in patients with irritable bowel syndrome. *Medicine.* 2017;96(51):e9235.

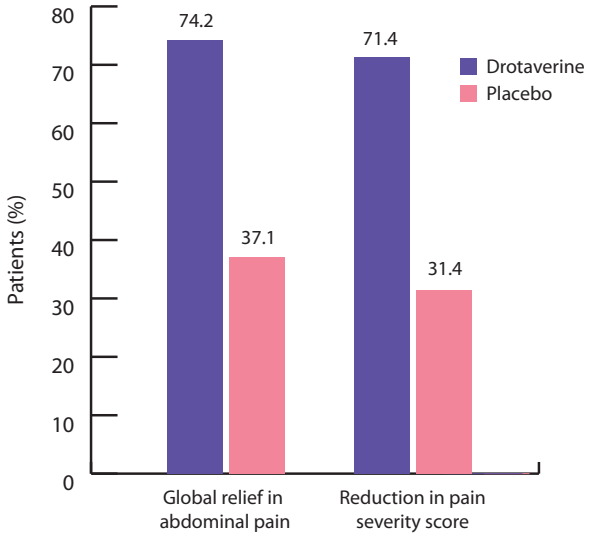
Rai RR and colleagues,[22] in a randomized placebo-controlled study conducted across three health-care centers in India, demonstrated that treatment of abdominal symptoms related to IBS with Drotaverine HCl 80 mg given three times daily for 4 weeks is more effective than placebo. Pain frequency decreased 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 2). Pain severity scores

Figure 2: Proportion of patients experiencing reduction in pain frequency with Drotaverine versus placebo



Adapted from: Rai RR, Dwivedi M, Kumar N. Efficacy and Safety of Drotaverine Hydrochloride in Irritable Bowel Syndrome: A Randomized Double- Blind Placebo-Controlled Study. *Saudi Journal of Gastroenterology.* 2014;20(6):378-82.

Figure 3: Symptomatic improvement in irritable bowel syndrome with Drotaverine versus placebo



Adapted from: Misra SC, Pandey RM. Efficacy of drotaverine in irritable bowel syndrome: A double blind, randomized, placebo-controlled clinical trial. *Am J Gastroenterol.* 2000; 95 (9):2544.

also decreased significantly in the Drotaverine group [66 (77.7%)] as compared to placebo [26 (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.

In another Indian study, Misra and Pandey[28] demonstrated that Drotaverine (80 mg thrice daily) produces global improvement in abdominal pain in IBS. At the end of 2 and 4 weeks of treatment, pain frequency decreased in 11 (31.4%), and 25 (71.4%) patients, in the Drotaverine group, respectively, as compared with decrease in 2 (5.7%), and 11 (31.4%) patients in the placebo group ($p < 0.001$). A significant reduction in pain severity score was also observed in the Drotaverine group (71.4%), as compared with placebo (31.4%), at 4 weeks ($p < 0.001$) (Figure 3). Global relief in abdominal pain as perceived by the patient and the clinician was 74.2% in the Drotaverine group, as compared with 37.1% in the placebo group ($p < 0.001$). Patients in the Drotaverine group also reported a considerable improvement in stool frequency (25.7%) in comparison to placebo group (2.8%).

Conclusion

Irritable bowel syndrome is a functional gastrointestinal disorder that presents as a major public health concern due to its high prevalence, social and economic burden and its ability to impair health-related quality of life. Owing to a diverse symptomatology, therapeutic management is challenging and necessitates comprehensive management strategy. Symptomatic treatment, with the aim of achieving global symptom resolution, is the mainstay of therapeutic management. Since abdominal pain is one of the most commonly encountered and vexing symptoms of irritable bowel syndrome, it is reasonable to use antispasmodic drugs in patients with IBS. Antispasmodic agents alleviate spasms, cramps and pain in patient with regulation of intestinal motility. Drotaverine, an antispasmodic agent has been shown to be effective in this context since it is shown to normalize the GI motility. Drotaverine exerts a good relaxing effect on intestinal smooth muscle, resulting in pain alleviation. Additionally, advantageous properties of Drotaverine, including lack of anticholinergic side-effects, make it an ideal candidate for treatment of bothersome symptoms in irritable bowel syndrome.

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