Irritable Bowel Syndrome in Light of Functional Gastrointestinal Disorder Management

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Functional Gastrointestinal Disorders

Functional gastrointestinal disorders (FGID) continue to be a prevalent set of conditions faced by the healthcare team. This complex set of disorders has a significant emotional and economic impact. FGIDs, such as functional dyspepsia (FD) or irritable bowel syndrome (IBS), are characterized by chronic or recurrent abdominal symptoms of pain.[1]

Although gastrointestinal symptoms are highly prevalent in FGID, there remains no organic explanation for the symptoms in most of the patients. Most of these people will be labelled as having an FGID, such as IBS, FD, or functional constipation. These conditions affect up to 40% of people at any one point in time. Among them two-third usually have chronic, fluctuating symptoms.[2]

Symptoms

It is noteworthy that FGIDs are diagnosed solely by symptomatology as there is a lack of understanding of the underlying structural or chemical abnormalities. The main symptoms described by patients with FGIDs include abdominal pain, dyspepsia, regurgitation, bloating, constipation, diarrhea, incontinence, problems in the passage of food or stool, or any combination of these symptoms.[3] Patients with FGIDs, along with having symptoms related to the gastrointestinal tract, have co-existing psychosocial symptoms such as stress, anxiety and depression as well.[3] Psychological comorbidity is common; however, whether or not this predates, or is driven by, symptoms remain elusive.[2]

Pathophysiology

The pathophysiology of FGID is complex. In recent years, a number of mechanisms have been explored such as gut-brain axis, effects of diet, genetic factors, infections and disturbances in the intestinal microbiota, low-grade mucosal inflammation, immune activation, altered intestinal permeability, disordered bile salt metabolism or abnormalities in 5-hydroxytryptamine (5-HT) metabolism. Environmental factors also appear to play the role in its pathophysiology.[1]

Irritable Bowel Syndrome: A Highly Prevalent FGID

IBS is a highly prevalent FGID that displays a wide range of symptoms of gastrointestinal dysmotility and visceral hypersensitivity. It is characterized by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits.[4] IBS affects 7% to 21% of the general population. It is a chronic condition that can substantially reduce quality of life and work productivity.[5]

Diagnostic Approaches in IBS

The clinical diagnosis of IBS is mainly based on a detailed history and examination of the patients. In most cases with typical symptoms, detailed diagnostic investigations, including colonoscopy, are generally not required to make a diagnosis, especially if there is no serious sign.[6,7]

The New Rome IV Diagnostic Criteria for Irritable Bowel Syndrome

The new Rome IV has introduced certain changes in the Rome III criteria. The new Rome IV now requires that patients have abdominal pain and the term discomfort is now eliminated. The reasons for this change are as follows: Discomfort is considered nonspecific and ambiguous term and eliminating discomfort from the criteria brings the diagnostic criteria into closer alignment with the US FDA's guidance on evaluating IBS. As such, only abdominal pain is now included that should be present at least one day per week during the previous three months, whereas only 3 days per month were required in Rome III. Moreover, because not in every patient abdominal pain coincide with stool changes, onset is now deleted from the Rome IV.[6,8-10]

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.[11]

Association Between Lactose Intolerance and IBS

IBS and lactose intolerance may present with similar symptoms and both conditions are common worldwide. Patients with IBS have been found to have considerably more subjective lactose intolerance complaints (abdominal pain, bloating, distension, flatulence, and diarrhea) as compared to those without IBS, and to have increased likelihood of lactose malabsorption than the general population.[12,13] 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.[14-17]

Symptomatic Management of IBS based on the Treatment-Principles of FGID

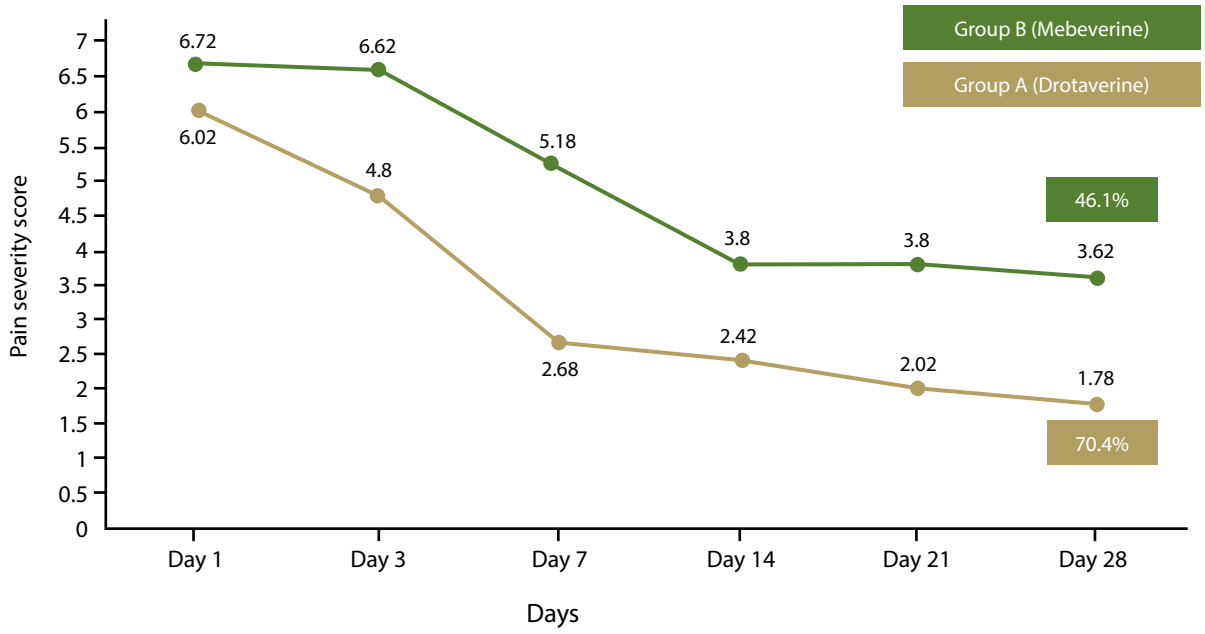
Abdominal pain is one of the most commonly encountered and vexing symptoms of IBS, and it is considered among the most frequent reasons of seeking medical care. This functional association is especially pertinent in the setting where chronic abdominal pain is associated with abnormality in stool consistency 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.[18,19]

Drotaverine: An Antispasmodic Treatment Modality for IBS

Antispasmodic drugs have been and remain the main stay of therapy and these agents have demonstrated good symptom relief.[20] Drotaverine is one such 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.[20,21] 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.[22]

Drotaverine is a potent spasmolytic or antispasmodic drug which acts directly on the smooth muscles by inhibiting phosphodiesterase IV enzyme and calmodulin, which is considered to regulate the smooth muscle relaxation of the gastrointestinal tract. Drotaverine directly normalizes the dysmotility of intestinal tract. It suits all subset of IBS patients, the diarrhea predominant as well as the constipation predominant. Drotaverine is well tolerated and provides global relief from abdominal pain

Figure 1: Change in Pain Severity Score in patients with IBS with drotaverine versus mebeverine therapy



in IBS. 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.[23-25]

Evidence-Based Efficacy of Drotaverine

Rai and Nijhawan[26] 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 1). 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 (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.

Misra *et al*[23] conducted a prospective double blind, randomized study, wherein 70 patients with IBS 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

Figure 2: Reduction in pain frequency with drotaverine versus placebo in patients with IBS

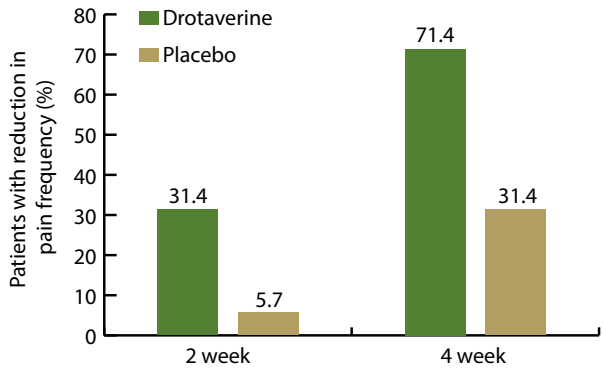
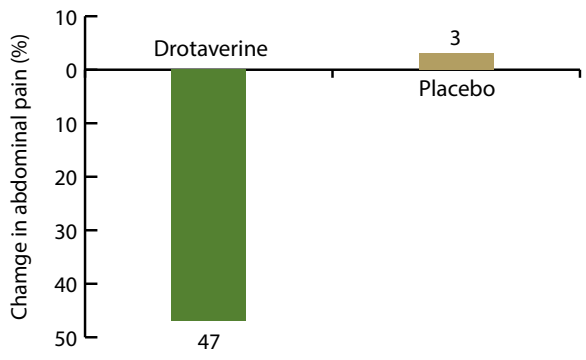


Figure 3: Change in abdominal pain from baseline with drotaverine versus placebo in patients with IBS



in the drotaverine group experienced reduction in pain frequency, compared to 11 (31.4%) patients in the placebo group (Figure 2). 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 movements.

In another double blind, randomized, placebo control study, conducted among 62 patients with IBS and constipation, Pap and colleagues[24] 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 3). 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.

Rai and colleagues[20] 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 4). 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. Therefore, this study suggested that treatment of abdominal symptoms related

Figure 4: Patients experiencing reduction in pain frequency with drotaverine versus placebo

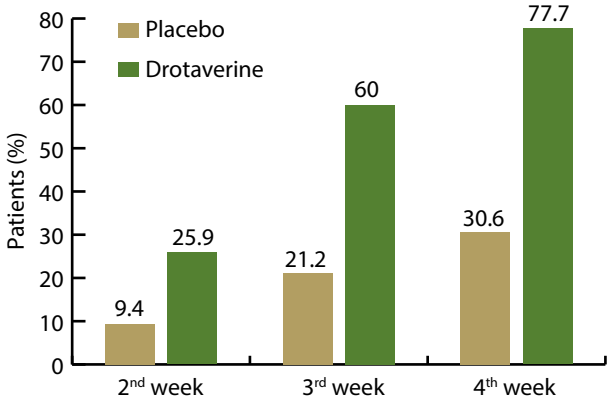
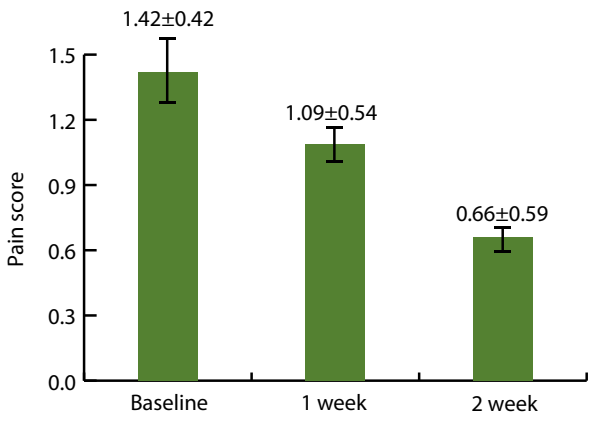


Figure 5: Pain scores before and after drotaverine therapy in patients with IBS



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

Sun J *et al*,[27] 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 5). 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.

Xue XC *et al*[28] 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) 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). In a nutshell, this study suggests that drotaverine is a promising therapeutic agent to alleviate symptoms of irritable bowel syndrome.

Drotaverine, owing to its clinical efficacy and well-tolerability, has also been recommended by various international guidelines for symptomatic improvement in patients with IBS (Table 2).[29-31]

Table 1: 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

Table 2: Guidelines suggesting the use of drotaverine for IBS

Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome (IBS) 2019
• Subanalyses of individual antispasmodics demonstrated significant benefits compared with placebo for drotaverine, otilonium, pinaverium bromide, hyoscine bromide, and cimetropium bromide
American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome, 2018
• It is suggested to use certain antispasmodics (Drotaverine, otilonium, pinaverium, hyoscine, cimetropium, and dicyclomine) for overall symptom improvement in IBS patients
Guidelines on the management of irritable bowel syndrome, 2018 (Poland)
• It is suggested to use certain antispasmodics, the efficacy of which in IBS has been confirmed, such as hyoscine and drotaverine rather than antispasmodics as a group

End Note

Irritable bowel syndrome is one of the highly prevalent functional gastrointestinal disorders displaying symptoms of gastrointestinal dysmotility and visceral hypersensitivity. With a wide array of symptoms, IBS often manifests with abdominal pain, discomfort such as cramping, bloating, gas, diarrhea, and/or constipation. The underlying cause of abdominal pain in functional gastrointestinal disorders including IBS has been conventionally attributed to smooth muscle spasm. Lactose intolerance may also present symptoms similar to 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. Considering that recurrent abdominal pain is the central feature of IBS, use of smooth muscle relaxants is deemed beneficial. 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 all subtypes of IBS. Drotaverine is well tolerated and provides global relief from abdominal pain in IBS. It does not have side effects similar to anticholinergics. A large pool of studies has substantiated the effectiveness of drotaverine in improving the abdominal symptoms related to irritable bowel syndrome, such as stool frequency, consistency, urgency, and flatulence.

References

1. Holtmann G, Shah A, Morrison M. Pathophysiology of Functional Gastrointestinal Disorders: A Holistic Overview. *Dig Dis.* 2017;35 Suppl 1:5-13.
2. Black CJ, Drossman DA, Talley NJ, *et al*. Functional gastrointestinal disorders: advances in understanding and management. *Lancet.* 2020 Nov 21;396(10263):1664-1674.
3. Mukhtar K, Nawaz H, Abid S. Functional gastrointestinal disorders and gut-brain axis: What does the future hold?. *World J Gastroenterol.* 2019;25(5):552-566.
4. Pae CU, Lee SJ, Han C, Patkar AA, Masand PS. Atypical antipsychotics as a possible treatment option for irritable bowel syndrome. *Expert OpinInvestig Drugs.* 2013 May;22(5):565-72.
5. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA.* 2015 Mar 3;313(9):949-58.
6. Lacy BE, Patel NK. Rome Criteria and a Diagnostic Approach to Irritable Bowel Syndrome. Weber HC, ed. *Journal of Clinical Medicine.* 2017;6(11):99.
7. El-Salhy M. Irritable bowel syndrome: diagnosis and pathogenesis. *World J Gastroenterol.* 2012;18(37):5151-63.
8. Schmulson MJ, Drossman DA. What Is New in Rome IV. *J Neurogastroenterol Motil* 2017;23:151-163.
9. Whitehead WE, Palsson OS, Simrén M. Irritable bowel syndrome: What do the new Rome IV diagnostic guidelines mean for patient management? *Expert Rev Gastroenterol Hepatol.* 2017;11(4):281-283.
10. Longstreth GF, Thompson WG, Chey WD, *et al*. Functional bowel disorders. *Gastroenterology* 2006;130:1480-1491.
11. Konturek PC, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. *J PhysiolPharmacol.* 2011;62(6):591-9.
12. Saha L. Irritable bowel syndrome: Pathogenesis, diagnosis, treatment, and evidence-based medicine. *World J Gastroenterol.* 2014;20(22):6759-73.
13. Xiong L, Wang Y, Gong X. Prevalence of lactose intolerance in patients with diarrhea-predominant irritable bowel syndrome: data from a tertiary center in southern China. *J Health PopulNutr.* 2017;36(1):38.
14. Bolin T. IBS or intolerance? Aust Fam Physician. 2009;38(12):962-5.
15. Böhmer CJ, Tuynman HA. The effect of a lactose-restricted diet in patients with a positive lactose tolerance test, earlier diagnosed as irritable bowel syndrome: A 5-year follow-up study. *Eur J Gastroenterol Hepatol.* 2001;13(8):941-4.
16. Deng Y, Misselwitz B, Dai N. Lactose Intolerance in Adults: Biological Mechanism and Dietary Management. *Nutrients.* 2015;7(9):8020-35.
17. Natural & Safe management of Lactose Intolerance. Available at: http://www.yamoo.org/. Accessed on 13/08/2021.
18. El-labban GM, Hokkam EN. The efficacy of laparoscopy in the diagnosis andmanagement of chronic abdominal pain. *J Minim Access Surg*. 2010; 6(4): 95–99.
19. Grover M. When is irritable bowel syndrome not irritable bowel syndrome?Diagnosis and treatment of chronic functional abdominal pain. *CurrGastroenterol Rep.* 2012;14(4):290-6.
20. 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):378-382.
21. Mishra SC, Gupta K, Chatterjee N. Drotaverine in irritable bowel syndrome: A clinical review. *Gastroenterology Today.* 2001;5(4):186-188.
22. Blasko G. Pharmacology, mechanism of action and clinical significance of a convenient antispasmodic agent. *JAMA India.* 2001;4(12):55-6.
23. 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.
24. Pap A, Hamvas J, Filiczky I, *et al*. Beneficial effect of drotaverine in irritable bowel syndrome (IBS). *Gastroenterology.* 1998;114(Suppl 1):A818.
25. Abdullah M, Firmansyah MA. Diagnostic approach and management of acute abdominal pain. *Acta Med Indones.* 2012 Oct;44(4):344-50
26. Rai 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 Feb 24.
27. Sun J, Yuan Y, Gao J, *et al*. Treatment of irritable bowel syndrome with drotaverine hydrochloride: A multicentre clinical trial. *Chinese Journal of Gastroenterology.* 2010; 15(12):735-7
28. Xue XC, Qi XX, Wan XY. Randomized controlled study of efficacy and safety of drotaverine hydrochloride in patients with irritable bowel syndrome. *Medicine.* 2017 Dec;96(51):e9235.
29. Ford AC, Moayyedi P, Chey WD, *et al;* ACG Task Force on Management of Irritable Bowel Syndrome. American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome. *Am J Gastroenterol.* 2018;113(Suppl 2):1-18.
30. Pietrzak A, Skrzydło-Radomańska B, Mulak A, *et al.* Guidelines on the management of irritable bowel syndrome: In memory of Professor Witold Bartnik. *Prz Gastroenterol.* 2018;13(4):259-88.
31. Moayyedi P, Andrews CN, MacQueen G, *et al*. Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome (IBS). *Journal of the Canadian Association of Gastroenterology.* 2019;2(1):6-29.