Advances In Diagnosis And Pain Management Of Inflammatory Bowel Disease

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Overview

Inflammatory bowel disease (IBD) consist of two types of chronic intestinal disorders namely Crohn's disease and ulcerative colitis.[1] Crohn's disease is a transmural inflammation affecting any part of the gastrointestinal tract, most commonly terminal ileum and the perianal region. It is frequently associated with complications including abscesses, fistulas and strictures. On the contrary, ulcerative colitis is characterized by mucosal inflammation and is restricted to the colon (Table 1).[1,2] The incidences of ulcerative colitis and Crohn's disease are highest in the West with annual rates of 24.3 per 100,000 and 29.3 per 100,000 persons, respectively. However, with rapid urbanization their incidence is also rising in parallel in the Asian countries. Nevertheless, all the developed countries in Asia do not share a similar incidence. India leads the Southeast Asian countries with an escalating incidence and prevalence of IBD.[3,4] Near about 25% of patients with IBD are diagnosed in the first 2 decades of their life, among which majority of them are diagnosed in their childhood with an increased incidence in the early second decade of life. Furthermore, various studies have also demonstrated an increased incidence of IBD; particularly in adolescents.[5] The exact etiology of IBD is unknown; however, the environmental factors, genetic factors and immune responses have been considered to be involved and functionally integrated in the pathogenesis.[6]

According to the results of multiple studies, the development of IBD occurs due to an exaggerated or insufficiently suppressed immune response to a hitherto undefined luminal antigen, derived from microbial flora. This inflammatory process then damages the mucosa, which further disturbs the epithelial barrier function leading to an increased influx of bacteria into the intestinal wall, thereby further accelerating the inflammatory process.[7] Considering the diversified pathogenesis of the disease, there exist a need for an assured curative therapeutic regimen.[8] Patients having IBD usually follow a lifelong relapsing and remitting course which affects their quality of life and results in long-term sequelae. Optimal diagnosis and treatment by healthcare providers can possibly help in preventing complications. This entails the need for advancements in the continuous and comprehensive care for IBD patients.[9]

Table 1: Key features in Crohn's disease and ulcerative colitis

Key features	Crohn's disease	Ulcerative colitis
Involvement of		
• Upper parts of GIT	Rarely	Never
• Distal Ileum	Very common	Never
• Colon	Common	Always
• Rectum	Rarely	Never
Signs and symptoms	• Pain in the lower right abdomen • Swelling • Thickening of the bowel wall	• Pain in the lower left abdomen • Diarrhea • Weight loss • Rectal bleeding

Source: Fakhoury M, Negrulj R, Mooranian A, Al-Salami H. Inflammatory bowel disease: clinical aspects and treatments. *Journal of Inflammation Research*. 2014;7:113-120.

Diagnostic And Evaluative Advances

The diagnostic evaluation of IBD is a challenging task especially in cases where the disease is limited to the small bowel. The disease is often mistaken by other conditions including Crohn's disease and food intolerance due to the vague and overlapping symptoms mainly occurring at a young age. A limited access to the gastroenterologists and resources leads to a deferral of several months in diagnosing the condition which eventually results in earlier disease-related complications. Recent advancements in the diagnostic techniques constitute an adjunct investigational means to the standard ileocolonoscopy. The current key investigations in the diagnosis include magnetic resonance (MR) and computed tomographic enterography (CTE).[9] However, a combination of symptoms-based assessment, excluding overlapping gastrointestinal diseases and positive biomarkers also appears to aid in diagnosing IBS.[10]

Evaluative Advances

Serological Markers

- Various serological markers have been found to be associated with IBD. These markers have been widely used to discriminate between IBD and irritable bowel syndrome (IBS). Additionally, it is also used to diagnose the subtypes of IBD, phenotypes of Crohn's disease, prognostication of disease, prediction of the disease course and the need for surgery in both adult and pediatric patients. Commonly used markers include antibodies to the outer membrane porin of *Escherichia coli*

(OmpC-IgG), *Pseudomonas fluorescens* (anti-I2), and flagellin (anti-CBir1), whereas the anti-glycan antibodies include anti-Saccharomyces cerevisiae (ASCA), antilaminaribioside (ALCA), anti-chitobioside (ACCA), anti-mannobioside (AMCA), anti-laminarin (anti-L), and anti-chitin (anti-C) antibodies. Among these antibodies, majority have been associated with Crohn's disease. In contrast, markers for ulcerative colitis include anti-neutrophil cytoplasmic antibodies (pANCA), antibodies against goblet cells (GAB), anti-proteinase 3 (anti-PR3), high mobility group box 1 and box 2 non-histone chromosomal proteins (HMGB1 and HMGB2) (Box 1).[9, 11]

BOX 1: Serological markers of irritable bowel disease

Antibodies to microbial antigens	Autoantibodies
Anti-glycan antibodies (ASCA, ACCA, ALCA, AMCA, Anti-L, Anti-C)	pANCA
Anti-OmpC	PAB
Anti-I2	GAB
Anti-Cbir1	

Abbreviations: ASCA - Anti-Saccharomyces cerevisiae antibodies; ACCA -antichitobioside carbohydrate antibodies; ALCA - antilaminaribioside carbohydrate antibodies; AMCA - anti-mannobioside carbohydrate antibodies; Anti-L - anti-laminarin antibodies; Anti-C - anti-chitin antibodies; Anti-OmpC - antibody to outer membrane porin C; Anti-I2 - antibody to *Pseudomonas fluorescens* - associated sequence I2; Anti-Cbir1 - antibody to bacterial flagellin; pANCA -anti-neutrophil cytoplasmic antibodies; PAB - antibodies against exocrine pancreas; GAB - antibodies to goblet cells.

Source: Kuna AT. Serological markers of inflammatory bowel disease. *Biochemia Medica*. 2013;23(1):28-42.

Genetic Markers

- In addition to the serological markers, genetic factors also play a significant role in determining the susceptibility of IBD. It not only constitutes the etiology for IBD but also plays a significant role in the phenotype as well as disease progression. Various new genes have been identified to be involved in the genetic susceptibility to IBD. The characterization of genes aids in the identification of therapeutic agents and clinical assessment of phenotype and prognosis in patients with IBD. The multiple functional polymorphisms of the interferon regulatory factor 5 (IRF5) gene are associated with systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, multiple sclerosis, psoriasis and IBD. Besides, IRF5 polymorphisms were also found to affect the risk profile for Crohn's disease and ulcerative colitis in conjunction with ancestry and nucleotide oligomerization domain 2 (NOD2) genotypes. The development in the field of molecular biology tools (microarrays, proteomics and epigenetics) have progressed the field of genetic markers discovery. Additionally, the advances in the bioinformatics in conjunction with cross-disciplinary collaborations have greatly enhanced the ability to retrieve, characterize and analyze large amount of data generated by the technological advances.[9,12]

Non-Invasive Inflammatory Markers

- Non-invasive inflammatory markers are now considered as an essential element of the daily assessment of patients with IBD. These markers helps in making initial diagnosis, differentiating between IBD and other diseases, evaluating the symptoms of active IBD to rule out flare ups, postoperative evaluation, therapeutic response and predicting relapse. Previously used inflammatory markers have now been discontinued since they are generally non-specific and new markers which are more specific to the GI tract, such as fecal calprotectin (FC) and stool lactoferrin (SL), have been introduced.[9]

Imaging Advances

Magnetic Resonance Imaging

- Magnetic resonance imaging (MR) is considered as a promising investigatory tool for adult patients with IBD. It is a non-invasive method and do not have ionized radiations making it more suitable to use in IBD patients which require repeated examinations. A neutral contrast medium is used in the MR procedure which can be given either orally (enterography) or through a naso-enteric tube inserted under fluoroscopic guidance (enteroclysis). MR enteroclysis is more accurate in diagnosing early disease and ensures more constant luminal distension in comparison to simple MR enterography. It can be used both as initial and follow-up examination in adults as well as pediatric patients suspected of having Crohn's disease since it allows accurate assessment of both the proximal and distal small bowel. Limitations of MR include its high cost, longer examination times, lower spatial resolution, and variable image quality.[9,13]

Computed Tomographic Enterography

- Computed tomographic enterography (CTE) is equally effective to MR enterography in the detection of disease activity and bowel damage in Crohn's disease, as well as extraluminal complications, particularly intra-abdominal abscess, but is less effective in depicting intestinal strictures as well as fistulae and sinus tracts. It has been validated as one of the primary diagnostic imaging tool in the evaluation of patients with IBD. It is particularly used in acute and emergency setting due to its availability and shorter examination time.[9,14]

Small Bowel Ultrasound

- Small bowel ultrasound is a safe and inexpensive imaging modality which is particularly used to detect small bowel abnormalities. It can also be used as the first-line imaging procedure in patients with a low suspicion of IBD. The major limitations of ultrasound is that its diagnostic accuracy in Crohn's disease is highly dependent on the level of experience of the radiologist as well as the location of disease, with lower accuracy for the disease proximal to the terminal ileum with a missed rate of up to 67%. However, the advancements with the use of Color Doppler ultrasound and contrast-enhanced ultrasound permits more enhanced imaging results.[9]

Endoscopic Advances

Endoscopic assessment with tissue sampling is the most valuable tool for primary diagnosis of IBD. The technique aids in improved observation of mucosal details, which helps in evaluating the extent of the disease. It also assesses the treatment efficacy in

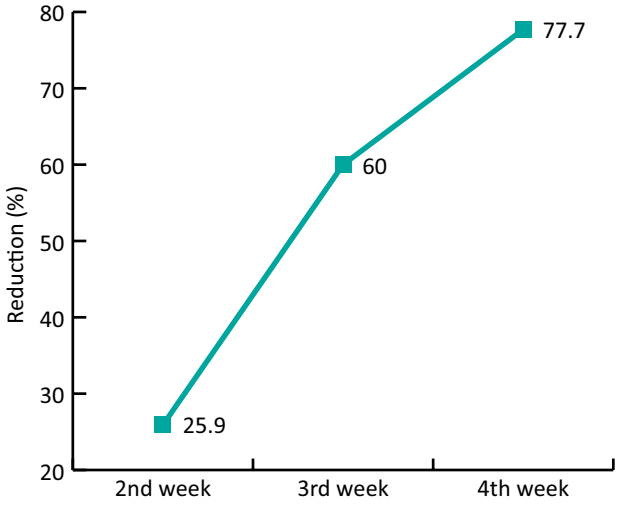
Table 2: Endoscopic techniques categories for inflammatory bowel disease diagnosis

Category	Endoscopic technique
White light endoscopy	• Standard definition colonoscopy • High definition colonoscopy • Water immersion colonoscopy
Dye-based image enhanced endoscopy	Chromoendoscopy with absorptive agents, contrast agents, tattooing, reactive staining agents
Dye-less image enhanced endoscopy	• Narrow band imaging • i-Scan • Autofluorescence imaging
Other emerging endoscopic techniques	• Confocal laser endomicroscopy • Balloon assisted enteroscopy • Endocytoscopy • Molecular imaging • Spectroscopy

Source: Cheon JH. Advances in the Endoscopic Assessment of Inflammatory Bowel Diseases: Cooperation between Endoscopic and Pathologic Evaluations. *Journal of Pathology and Translational Medicine*. 2015;49(3):209-217.

terms of mucosal healing and the risk of post-surgical recurrence. Evolution of endoscopic techniques has lead to reduced random biopsies due to its improved observation of mucosal details. These techniques include enhancement of image with modifying conventional endoscopy and mucosal imaging improvement with magnification or several optical techniques (Table 2). Every endoscopic technique is at a different stage of development and has special use. All advanced endoscopies have their own advantages and limitations. Therefore, it requires more experience before implementing them in clinical practice and cautious use for patients on clinical use.[9,15]

Figure 1: Reduction in pain frequency with drotaverine in pateints with irritable bowel syndrome



Source: 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 : Official Journal of the Saudi Gastroenterology Association*. 2014;20(6):378-382.

Medical Advances

Lactose Intolerance In Inflammatory Bowel Disease

Patients with IBD usually experience lactose intolerance. Near about one-third of the individuals retain the ability to digest lactose (LP; lactase persistence, lactose digesters) while the rest lose it [LNP; lactase non -persistence, lactose maldigesters LM)]. The condition can be objectified accurately by H2 lactose breath testing.[16,17] A comprehensive study aimed at identifying the prevalence of lactose intolerance in IBD patients. The study used genetic marker $CC_{13910,}$ on chromosome2 for the evaluation of sensitivity to lactose. Results reported that approximately 70% of patients IBD affected from lactose sensitivity.[18] Despite, lactose intolerance being a common occurrence in patients with IBD, the relationship between lactose rich diet and IBD is controversial. However, some studies have evinced that lactose- rich diet can protect against IBD. Cutting down lactose products, might impact adversely on bone and colonic complications.[16] Diagnosis and management of lactose intolerance is an important consideration in the management of IBD.[19] Lactose intolerance depends not only on the expression of lactase but also on the dose of lactose, intestinal flora, gastrointestinal motility, small intestinal bacterial overgrowth and sensitivity of the gastrointestinal tract to the generation fermentation products of lactose digestion. Its management generally includes lactose-reduced diet and enzyme replacement. Lactase enzyme aids in digestion of lactose-rich products in IBD patients with lactose intolerance, which in turn improves patient compliance.[20]

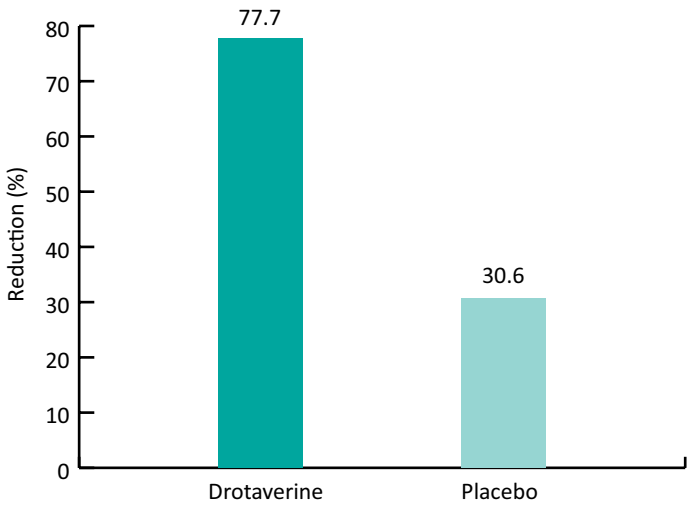
Pain Management In Inflammatory Bowel Disease

Management of pain in IBD is a critical task, due to the complex interplay between multiple factors leading to pain generation and its significant consequences. However, due to advancements in medical treatments for IBD, there is a growing recognition of functional abdominal pain within the IBD population. The clinicians should recognize and appreciate the potential overlap symptoms associated with IBD and should therefore customize the pain management in these patients. Since abdominal pain is one of the cardinal features of intestinal inflammation, use of standard treatment regimes can alleviate inflammation-related pain in majority of patients. These include the use of aminosalicylates, antibiotics, corticosteroids, enteral therapy, immunomodulators, and biological response modifiers.[21]

Role Of Antispasmodic Agents: Focus On Drotaverine

Antispasmodic agents are able to provide a bridge of pain relief even if the standard medical therapies are unable to control inflammation. Since pain from inflammation or

Figure 2: Elevated psychological traits in patients with irritable bowel syndrome



Source: 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 : Official Journal of the Saudi Gastroenterology Association.* 2014;20(6):378-382.

partial obstruction generally manifests with intestinal spasms, anticholinergic antispasmodic medications are commonly employed as analgesic agents. They have established efficacy in the treatment of abdominal pain in IBD. Antispasmodic agents appear to be a reasonable choice for the management of pain associated with inflammation or partial obstruction.[21] In this context an antispasmodic agent named drotaverine (a selective inhibitor of phosphodiesterase (PDE) isoenzyme IV), has been found to be useful in spastic and motility disorders of the smooth muscles in adults. Further, a randomized placebo-controlled trial was conducted to evaluate its efficacy in the control of functional abdominal pain in children. Results reported that drotaverine hydrochloride is an effective and safe pharmaceutical agent in the management of recurrent abdominal pain in children.[22]

Results of the above trial were supported by a multicentric, randomized, double-blind, placebo-controlled parallel group study23 which demonstrated the efficacy and safety of drotaverine hydrochloride in the symptomatic relief of patients with irritable bowel syndrome. The study include a total number of 180 patients with irritable bowel syndrome who were randomized to receive either drotaverine hydrochloride (80 mg, thrice a day) or placebo, for a period of 4 weeks. The duration of abdominal pain and stool frequency were measured every week in both the groups. Study results divulged that pain frequency was considerably decreased in 22 (25.9%), 51 (60%) and 66 (77.7%) patients in the drotaverine group at the end of 2nd, 3rd and 4th weeks respectively, in comparison to 8 (9.4%), 18 (21.2%), and 26 (30.6%) in the placebo group (Figure 1). The pain severity scores were also found to be reduced in the drotaverine group 66 (77.7%) when compared with placebo 26 (30.6%) after 4 weeks (Figure 2). Besides, the global relief in abdominal pain as perceived by the patient and the clinician in the drotaverine group was also more (85.9% vs 39.5% and 82.4% vs 36.5%, respectively) in comparison to the placebo. Overall drotaverine was found to be well tolerated without any major side effects..

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