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Pathophysiology and treatment of neurogenic constipation

Chanchal Garg, Saurabh Satija, Meenu Mehta, Nivedita, Munish Garg

Department of Pharmaceutical Sciences, Maharshi Dayanand University Rohtak, India

Abstract
Constipation is not a life threatening condition but it deteriorates quality of life and restricts patient's social activities, increases levels of anxiety and depression. In the condition of constipation patient may have rare evacuation ie. When faeces are evacuated less frequently than three times a week. Patient may report more subjective complaints like prolonged time of evacuation, hard stools or stools of low volume, sensation of incomplete evacuation, difficulty in expelling of even a soft stool and painful defecation. Neurogenic constipation occurs most commonly after spinal cord injury, multiple sclerosis and in Parkinson`s disease. In diagnosis, neurological and proctologic examinations are required followed by colonic transit time, defecography and anorectal manometry. Most of the patients respond positively on medical treatment. However, a small group of them requires surgical treatment in the form of either colostomy or ileostomy. Its treatment typically begins with lifestyle changes and fiber supplementation, alteration of fluid intake, dietary modification and physical activity. Patients can avail various emollient, osmotic and stimulant laxative. Newer therapies are options that may help to improve symptom relief and patient satisfaction. 5-HT_4 serotonin agonist and 5-HT_3 antagonist are available. The chloride channel activator lubiprostone is recently approved for the treatment.

Keywords: Lubiprostone; 5-HT_4 serotonin; Neurogenic Constipation

1. Introduction
Constipation is not a life threatening condition but it deteriorate quality of life and restrict patient's social activities, increases levels of anxiety and depression (Ng *et al.*, 2005) [32]. In the condition of constipation patient may have rare evacuation i.e. when faeces are evacuated less frequently than three times a week. Patient may report more subjective complaints like prolonged time of evacuation, hard stools or stools of low volume, sensation of incomplete evacuation, difficulty in expelling of even a soft stool and painful defecation (Jacek *et al.*, 2013). Constipation that continues for 3 months or longer is the most prevalent functional bowel disorder (O' keefe *et al.*, 1992) [33].

According to a survey the average population across the globe suffering from chronic constipation is around 10%. But the Indian statistics are a bit shocking. About 14% of the Indians suffer from chronic constipation, higher than the world average. The Gut-Health Survey conducted a study on 3500 people from 6 cities across the nation. As per the survey Coimbatore has the maximum number of people suffering from chronic constipation (21%), followed by Mumbai (19%), Kolkata and Delhi stand out equal taking occupying the third position (13%), Hyderabad at fourth position (6%) and Lucknow having the least number of sufferers (2%).

1.1 Epidemiology and predisposing factors
The highest reported incidences of constipation in specific populations were 45% of all patients with cancer (McMillan and Williams, 1989) [30], 45% of all frail elders (Wolfsen *et al.*, 1993) and 46% of all hospitalized elders (Wright, 1984). The incidence of constipation increases with age. Women's are reported constipated more often than men also its incidence increases in people with diminished functional and cognitive ability and in the frail elderly (Campbell *et al.*, 1993) [6]. It is also common problem in pregnancy and after childbirth or surgery.

Predisposing factors include lifestyles, iatrogenic causes and secondary causes. Fifty percent of persons with chronic constipation have abnormal rectal emptying, while the remainder have normal or slow transit problems (Surrenti *et al.*, 1995) [39]. Risky situation for acute constipation include imposed immobility, change in toileting habits, dietary changes, medication major opioids, polypharmacy and stress.

1.2 Pathophysiology of constipation
The colon absorbs water and electrolytes from the chyme and stores fecal matter until it eliminate. The colon wall contains the intrinsic components that include Auerbach's plexus and Meissner's plexus. Auerbach's plexus, also known as the intramuscular myenteric plexus, located between the longitudinal and circular muscle layers. Meissner's plexus is located in the submucosa; it generally controls gastrointestinal secretion and local blood flow, while Auerbach's plexus controls the gastrointestinal movements. The intrinsic component is also known as the enteric nervous system and its function is to coordinate much of the colonic wall movement that mixes and advances stool through the colon (Benevento and Sipski, 2002) [5]. Two types of movements occur in the colon. One is propulsive movement, or peristalsis, that occurs when a segment of the colon is excited by distension, causing a contractile ring around the colon. This ring moves forward, propelling forward any material in front of it. Effective peristalsis requires an active

myenteric plexus because peristalsis is weak if the myenteric plexus is congenitally absent, or if its function is inhibited by disease or anticholinergic medication. The second type of colonic movement is haustrations, or mixing, movements. When a portion of the colon wall becomes distended, the stretch of the intestinal wall elicits localized concentric contractions. These contractions slowly dig into and roll over the fecal material in the colon, exposing it to the surface of the large intestine, where fluid and dissolved substances are absorbed. The parasympathetic innervations are through the vagus nerve for the proximal colon and through the sacral parasympathetic nerves for the distal colon and rectum. The sympathetic innervation is from the thora columbar outflow. The extrinsic nerve supply terminates on the nerves of the intrinsic plexuses. If the colon is denervated of its external nerve supply, it is still capable of coordinated peristalsis through its intrinsic plexuses.

Movement of material through the colon depends on the combination of haustral contractions and mass movements. Most of the propulsion in the cecum and ascending colon results from slow, persistent haustral contractions, which may require 8 to 15 hours to move the chyme from the ileocecal valve through the transverse colon. During this time the chyme becomes fecal in quality and becomes a semisolid slush instead of a semifluid. At the transverse colon and through the sigmoid colon, mass movements take over the propulsive function. Mass movements usually occur only 1 to 3 times a day, usually after a meal. They are facilitated by the gastro colic and duodeno colic reflexes and are strongest for about 15 minutes in the first hour after breakfast. These mass movements are initiated when a constrictive ring forms in response to distension or irritation at a point along the colon, most frequently the transverse colon. This causes 20 cm or more of colon distal to the constrictive ring to lose its haustral contractions and contract instead as a unit. This action forces the fecal material in that segment down the colon. The series of mass movements persists for only 10 to 30 minutes, then returns in 12 hours, or even a day, later. When the mass movements have forced the feces into the rectum the need to defecate is felt.

Normal transit times through the colon vary greatly. Transit time can be measured clinically by radiopaque colonic transit time studies. Patients swallow 20 radiopaque markers and radiographs of the abdomen are taken to trace their passage through the colon. Persons with normal bowel function excrete 80% of the markers in 5 days (Hinton *et al.*, 1969) [20].

Central nervous system transmission of sensory input allows recognition of rectal fullness (Barnes and Lennard-Jones, 1985) [3]. This rectal distension causes reflex inhibition of the internal sphincter (Sun *et al.*, 1995) [38] through the myenteric plexus (Floyd and Wells, 1953) [11], thereby lowering the anal canal pressure. The puborectalis muscle and striated external anal sphincter that normally are tonic at rest and during sleep, contract reflexively upon rectal distension to maintain continence (Ihre, 1974). During normal defecation, the voluntary sphincters are inhibited (Park *et al.*, 1962) [34] through reflex or cortical pathways (Frenckner and Euler, 1975) [12] by the pudendal nerve and the S3 and S4 motor roots, which supply the puborectalis (Percy *et al.*, 1981) [36]. Relaxation of the puborectalis muscle widens and lowers the anorectal angle, which obliterates the flap valve effect of the angle while inhibition of the external anal sphincter relaxes the anal canal. The increase in the intra-abdominal pressure associated with rectosigmoid peristalsis permits rectal evacuation. Altered physiology factors such as slowed transit time, altered fecal composition, decreased ability to expel faeces and altered ability to acknowledge the urge to defecate may cause constipation.

2. Neurological disorder leading constipation

It is well known that the central nervous system (CNS) takes part in the control of visceral functions and its damage can lead to gastrointestinal impairment (Badiali *et al.*, 2000) [1]. Lesions affecting the pontine defecatory centre may disrupt the sequencing of sympatical and parasympathical components of defecation and impair the coordination of the peristaltic wave and the relaxation of the pelvic floor and external sphincter (Lim *et al.*, 2015; Winge *et al.*, 2003) [28, 41].

Constipation in stroke:- "The intestinal brain" is a term used for intestinal nervous system, which consists of numerous sensory, connecting and motor cells, including myenteric Auerbach's plexus, located between two layers of muscularis and submucosal plexus of Meissner. The bipolar fibers of Meissner's plexus, linked at one end to the sensory fibers running from the receptors of mucosa and the muscularis, represent the centripetal arm of the reflex arch (Jacek *et al.*, 2013). The fibers of the myenteric plexus are positioned at the end of the centripetal arm in the reflex arch and they release directly functional potential of myocytes responsible for contractile action of the bowel (Gabella, 1979) [13].

Spinal cord injury:- occurs mostly in young male patients after trauma such as, severe vehicle accidents and fatal water jumping (Pedersen *et al.*, 1989) [35]. Constipation is a clinical embodiment of large bowel dysfunction. The syndrome is called the upper motor neuron (UMN) bowel, if the lesion is located above the conus medullaris and lower motor neuron (LMN) bowel, if the lesion affects the conus, their axons in the cauda equina and pelvic nerves. Enfeeble symptoms are loss of voluntary control of defecation with threatening faecal incontinence, loss of rectal sensation and anal discriminatory properties (De Looze *et al.*, 1998) [8].

Multiple Sclerosis:- mostly patients suffering from multiple sclerosis complaint about constipation. Those multiple lesions are responsible for bowel dysfunction. Patient encounter the sign and symptoms akin to UMN and LMN bowel syndromes (Hinds *et al.*, 2006) [19].

Parkinson's diseases:- Dopamine is a basic neurotransmitter not only in central nervous system but also in the enteric nervous one. Its deficiency is responsible for the colonic motility in Parkinson's patients (Singrama *et al.*, 1995) [37]. Increased muscle tone is the characteristic to the patient's with Parkinson`s disease, also muscles of the pelvic floor including the puborectalis as well as the external anal sphincter. That is the cause of a rise except for a fall of the external anal

sphincter tone during defecation with faecal retention in the rectum (Lembo and Camilleri, 2003) [27]. Constipation is a risk factor for Parkinson's patient, bowel dysfunction can run as a basic disorder for many years in patient's (Krough *et al.,* 2008) [26].

3. Complications in Constipation

It includes anorexia, overflow incontinence, confusion, nausea, vomiting, urinary dysfunction, impaction, fissures, rectal prolapsed, haemorrhoids, bowel obstruction and syncope which may leads to anxiety and social isolation (Koch and Hudson, 2000) [25].

3.1 Physical Examination

- A complete abdominal assessment includes observation, auscultation, percussion and palpation. The presence or absence of distention, abdominal muscle tone, visible peristalsis, bowel sounds, borborygmi, masses, rigidity and tenderness should be measured.
- Rectal examination will detect fissures, haemorrhoids, masses, stool, prostate size and characteristic, perianal ulceration and anal sphincter tone which is best performed with the patient in the left lateral position (Ginsberg *et al.,* 2007) [15]. A vaginal examination should be performed to assess for a potential rectocele to female patient.
- Neurologic evaluation for anal reflex using a light pinprick or scratch should be performed.

4. Additional Evaluation

- Laboratory test: Fecal occult blood testing, thyroid function studies, serum electrolytes, serum glucose and complete blood count.
- Radiographic diagnostic testing: Testing of kidney, ureter and bladder may indicate to rule out an organic cause of constipation. If a positive occult blood test, weight loss, anemia and onset of constipation that cannot be attributed to lifestyle changes. Appropriate tests include a barium enema, a colonoscopy and a sigmoidoscopy.
- Failure to identify a cause for chronic constipation indicate the need for advanced evaluation ie. defeco graphy, pelvic floor electromyography, anorectal manometry, balloon expulsion tests, dynamic imaging, proctography, scintigraphic expulsion of artificial stool. Colonic transit tests include radiopaque marker transit test and intra luminal testing (Drost and Harris, 2006) [9, 17, 18].

5. Pharmacological management for constipation

- Laxatives are most commonly prescribed agents classified into four main types: bulking agents, stool softeners, stimulant laxative and osmotically active compounds.
- Bulking agents used in patients with episodic constipation when stools are lacking in water content. They are primarily organic polysaccharides which act by encouraging water retention in the stool. Ex- psyllium, bran, methycellulose, calcium polycarbophil (Emmanuel *et al.,* 2009) [10].
- Stool softeners are used for occasional constipation. They are anionic surfactants with an emulsifying and wetting action. Ex- docusate
- Stimulant laxatives, either naturally occurring agents like senna and cascara or phenolphthalein analogues like bisacodyl, which are hydrolysed in the gut by either enterocyte enzymes or colonic flora, and acting by stimulating peristalsis, sensory nerve endings which possibly interfere with electrolyte flux to inhibit water absorption. These agents are taken up by enterocytes and cause melanosis coli.
- Osmotic laxative act by generating an osmotic gradient which encourages water retention in the lumen. Both inorganic salts i.e. magnesium compounds and organic alcohols or sugars ie. lactulose and polyethylene glycol.
- 5-HT4 agonists: have important role in regulation of GI function. Activation of neuronal 5-HT4 receptors results in pro kinetic activity throughout GI tract and triggers the release of neurotransmitters from the enteric nerves resulting in increased contractility and stimulation of peristaltic reflex (Baker, 2005; Beattie and Smith, 2008; Gershon, 2005) [2, 4, 14]. Tegaserod is new class of compound called an aminoguanidine indole, a partial 5-HT_4 agonist which works by stimulating the peristaltic reflex and accelerate oral-cecal transit (Tougas *et al.,* 2002) [40] other medications are colchicines and misoprostol, they are reserved for severely constipated patients.
- 5-HT_3 antagonist, renzapride and mosapride and opioid antagonist such as methynaltrexone and alvimopan are used (Harris and Chang, 2006) [9, 17, 18].
- The chloride channel activator lubiprostone, it works on the apical side of the mucosal epithelial cell to increase fluid in the stool allowing spontaneous bowel movement which reduces abdominal pain, discomfort bloating and softens the stool (Harris *et al.,* 2006) [9, 17, 18].
- Neurotropic factor stimulate nerve activity growth and evaluated as a therapy for chronic constipation. Basically neurotrophin-3 evaluated as a treatment for Alzheimer's and Parkinson's disease (Crowell *et al.,* 2009) [7].

6. Conclusion

Constipation does not occur overnight and it is not reasonable to except that constipation can be relieved overnight. A well-balanced diet that includes fiber-rich foods, such as unprocessed bran, wholegrain bread, and fresh fruits and vegetable is must to avoid constipation. Present study reflected towards various patho-physiologic treatments of constipation focused on traditional and novel approaches for treatment.

7. References

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