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An Open Label, Randomized, Parallel Group Study To Compare the Efficacy and Safety of β-galactosido- sorbitol with β-galactosido-fructose in Treatment of Constipation.

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ABSTRACT

Constipation is a common complaint seen in clinical practice and usually refers to persistent, difficult, infrequent, or incomplete defecation. Different groups of drugs available for the treatment of constipations are, stimulant laxatives, bulk forming laxatives, emollient laxatives and osmotic laxatives. β-galactosido-fructose (lactulose) was one of the osmotic laxative used, recently β-galactosido-sorbitol (lactitol) is being promoted as an osmotic laxatives in the management of constipation, which has better palatability when compared to β-galactosido-fructose. It is an open label, randomized, parallel group,comparative study conducted in 90 patients of constipation. They were divided into two groups of 45 each. One group was given β-galactosido-sorbitol and the other β-galactosido-fructose. The study was conducted for duration of seven days. Patient's response to treatment was recorded in follow up visits, which included episodes of spontaneous bowel movement, side effects, palatability and patient's acceptability. The number of bowel evacuations among β-galactosido- sorbitol group was 9.30±1.09 when compared to 7.20±0.68 in β-galactosido-fructose group, being not significant ($p>0.05$). β-galactosido- sorbitol was significant in terms of less adverse effects when compared to β-galactosido-fructose group($p<0.05$).The patients in β-galactosido-sorbitol group had better response, found it more palatable and had better compliance in comparison to β-galactosido-fructose group. β-galactosido-sorbitol is less significant to β-galactosido-fructose in terms of bowel evacuations but more significant in terms of less adverse effects, palatability and compliance.

Keywords: Constipation, Osmotic Laxatives, β-galactosido-fructose, β-galactosido- sorbitol

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INTRODUCTION

Constipation is a common symptom of underlying gastrointestinal disorder affecting people of all age group[1]. Constipation is a subjective perception and may vary among different individuals. A physician may consider less than three stools per week as constipation whereas a patient may consider passage of hard stools, difficult and incomplete evacuation of stool as constipation [2]. The Rome III criteria , consensus definition used in research defines constipation as having two or more of the following for at least 12 weeks: straining in at least 25% defecations ,lumpy or hard stool in at least 25% defecations, sensation of incomplete evacuation in at least 25% defecations, sensation of anorectal obstruction / blockade in at least 25% defecations, manual manoeuvres to facilitate at least 25% defecations (e.g. digital evacuation, pelvic floor support),less than 3 defecations per week, presence of loose stools rarely without the use of laxatives, insufficient criteria for irritable bowel syndrome" [3].

The prevalence of constipation is more common in elderly people, reporting everyday use of laxatives. Advanced age is one of the risk factor for chronic constipation, with largest increase in prevalence after the age of 70 years. This can be due to effects of medication; immobility and blunted urge to defecate. The prevalence of constipation in women is 2 to 3 times more likely than men. Possible reasons include higher risk of injury to the pelvic floor from childbirth [4].

There are many etiological factors responsible for the development of the constipation. The factors may be physiological, endocrine abnormality, metabolic changes, drugs, neurological, psychological and any pelvic floor dysfunction [5]. Physiological factors like decreased physical activity or bed ridden for longer duration of time. Exercise has been promoted by many physicians as a first line of treatment as it causes changes in colonic motility [6]. Decreased intake of fluids and diet with less fiber may also lead to the development of constipation. Another important physiological factor is pregnancy, which may be associated with constipation. The development of constipation in pregnancy may be due to decreased fluid intake due to nausea and vomiting, decreased physical activity and also hormonal changes [7]. Most common endocrine abnormalities leading to constipation are hypothyroidism and diabetes mellitus. In hypothyroidism myxedematous infiltration of the gastro intestinal tract leading to decreased colonic transit time is the main cause [8]. In diabetes mellitus the autonomic nervous system dysfunction and decreased response of the gut mechanoreceptors may is the cause for the development of constipation [9]. The metabolic changes such as hypercalcemia and hypokalemia causes decreased contraction of the muscles of the wall of the gastrointestinal tract [5].

The intake of various drugs may end up in the development of the constipation. Most common drugs are antihypertensive preferably calcium channel blockers, anticholinergic, opioids, iron supplements, antacids containing aluminum and calcium etc [10]. Physical obstruction to the passage of the intestinal contents caused by any cancer or polyp to be considered for the development of constipation in the elderly people over fifty years. Pseudo intestinal obstruction may also present with constipation, which is due to myopathy of muscles of colon. Megacolon or mega rectum may also be one of the potential causes for constipation. They are more commonly acquired condition rather than congenital. One of the causes for megacolon or megarectum is Chaga's disease caused by the parasite *Trypanasoma Cruzi*. Hirshsprung's disease characterized by congenital narrowing of the colon due to aganglionic segment may also have constipation for life time [11]. Neurological cause for constipation include parkinsonism, spinal cord lesions and multiple sclerosis. In parkinsonism the depletion of the dopaminergic neurons in the myentric plexus leads to the development of constipation. Spinal cord lesions may lead to decreased contraction of the descending colon and decreased rectal sensation. In multiple sclerosis paradoxical puborectalis muscle contraction may be the cause for the development of constipation [12]. Psychological conditions like severe depression, anorexia nervosa and bulimia nervosa may also lead to development constipation [13].

The constipation can be treated by non-pharmacological interventions and pharmacological interventions. Non pharmacological interventions are most commonly considered as a first line of treatment in individuals with no other secondary cause responsible for constipation. They include increased intake of large fluids and fiber in the diet, regular exercise and bowel habit training. It is found that regular exercise will increase the intestinal colonic transit time [14]. Other interventions include bio feedback, behavioral therapy and electrical stimulation. Bio feedback therapy is reserved for the patients with pelvic floor muscle dysfunction. It involves the retraining of the pelvic floor muscle and anal sphincter with a balloon or electronic

probe. Electrical stimulation therapy wherein brief waves of electrical stimulation are applied, helps in the strengthening the muscles of the pelvic floor. The behavioral therapy which includes modification in the behavior is found to be helpful in patients with inflammatory disorder and also in women patients [15].

The pharmacological interventions include intake of the drugs for the treatment of constipation. These drugs can be classified depending upon the time taken to act as slow onset, intermediate onset and rapid onset. The other way of classifying would be by the mechanism of action of the drugs like bulk forming laxatives, stimulant laxatives, emollient laxatives, osmotic laxatives, chloride channel activator and prokinetic drugs [16].

The slow onset drugs will take two to three days for onset of action after regular consumption of drug. The drugs with slow onset of action include bulk forming laxatives, mineral oils and osmotic laxatives. The drugs with intermediate onset of action take six to twelve hours to act after a single dose and include saline laxatives, bisacodyl (oral), anthoquinones. Rapid onset drugs act within two to six hours and include drugs like castor oil, bisacodyl and glycerin rectal suppositories [17].

The bulk forming laxatives include methyl cellulose, agar agar, bran and plantago seeds (Isapgol).These are more commonly natural and semi synthetic polysaccharides and cellulose derivatives that are not digestible and adds to intestinal residual contents. They produce evacuation of solid or semisolid stools without irritation or gripping [18]. Stimulant laxatives are the other group of drug act by stimulating the large bowel. The drugs in this group are anthraquinone like cascara sargada and senna, castor oil, bisacodyl. The stools formed are semisolid and there may be incidence of gripping [19]. Emollient laxatives act by lubricating the formed stools and thereby decreasing the straining during defecation. It includes mainly liquid paraffin. Other edible oils like ground nut oil, coconut oil, cotton seed oil and corn oil can also be used as emollient laxative [20]. The chloride channel activators include lubiprostone and linaclotide. These drugs act locally in the gastro intestinal tract by opening the chlorine channels and there by secreting chloride rich intestinal fluid. They also accelerate the small intestinal and colonic transit time. The prokinetic drugs like tegaserod acts by agonist action on the 5HT4 receptors in the gastro intestinal tract and used most commonly in inflammatory bowel disease with predominant constipation [17].

Osmotic laxatives include certain salts, non-absorbable polysaccharides and some higher alcohol. The salts most commonly used are magnesium sulfate, magnesium hydroxide, magnesium carbonate, sodium potassium tartrate, sodium sulfate etc. These drugs exert osmotic effect and hold considerable amount of fluid and thereby increasing the intestinal bulk [21].

β-galactosido-fructose (Lactulose) an unabsorbed disaccharide has been used as osmotic laxative in the treatment of constipation. β-galactosido-fructose is excessively sweet and consequently is unacceptable by some patients. β-galactosido- sorbitol (Lactitol), a disaccharide analogue of β-galactosido-fructose has recently been described. This sugar is highly water soluble, less sweet than β-galactosido-fructose and is not absorbed in the human small intestine [22]. It has seemed that β-galactosido-sorbitol might have a potential as an alternative therapeutic agent to β-galactosido-fructose in the treatment of constipation. The present study was been undertaken to compare both efficacy and side effects of β-galactosido-sorbitol in comparison to β-galactosido-fructose in the treatment of constipation.

MATERIALS AND METHOD

This was an open label, parallel, comparative study conducted among ninety patients aged eighteen years and above with a history of constipation. Forty five patients were allotted to each β-galactosido- sorbitol group and β-galactosido-fructose group randomly.

Study included the patients aged eighteen years and above fulfilling the Rome III criteria for constipation. Patients with severe renal, hepatic insufficiency, suspected or diagnosed cancers, anal abscess, fissures, rectocele, irritable bowel syndrome, gastrointestinal obstructions and pregnant and lactating females were excluded from the study.

The patients belonging to each group was given the respective drug. The patients were advised to take the drug after the night meal or just before the going to bed for seven consecutive days. The patients

were instructed to consume drug orally 15ml/day as a single dose for the first three days and increase the dose to 30ml per day orally as a single dose for the next four days.

Follow up assessment was done for all patients on day four and day eight. The patients were enquired regarding spontaneous bowel movements or number of stool passed, number of stools passed with in twenty four hours and fourty eight hours following the first drug administration, frequency of enema, suppository or digital evacuation done in the study period. The assessment of taste and palatability was done by the patient himself as satisfactory, average or unsatisfactory. The relief of the subjective symptoms like pain, straining during defecation, belching, flatulence, consistency of stools, abdominal distension and sensation of incomplete evacuation were also enquired. The overall patient's response to drug was assessed as satisfactory, average or unsatisfactory.

Proportion of patients with the spontaneous bowel movement count of three or more at the end of the study period without use of any other laxatives were considered as complete response to treatment and set as primary end point. The secondary end point was proportion of patients with the spontaneous bowel movements with in twenty four hours and fourty eight hours of first drug administration .The assessment of safety and tolerability was done for the entire study period.

The statistical analysis was carried with the help of graph pad prism (version 5) to find out the significant difference between two laxatives. The study data was analyzed for the spontaneous bowel movements and incidence of adverse effects using unpaired student T test. $P<0.05$ was considered as significant.

RESULTS

Parameters	β-galactosido-sorbitol	β-galactosido-fructose
Spontaneous bowel movement/week	9.302±1.090%	7.209 ±0.6857%
Incidence of adverse reactions	27.16±3.923 %	42.93 ±5.122%
Consistency of stools	75.28%	67.05%
Satisfactory taste and palatability of drug	80.90%	48,86%
Overall patients acceptability of drug	80.90%	47.73%

The proportion of patients having spontaneous bowel movement count of three or more at the end of study period were being considered as complete response to treatment. It was found to be equal in both the study groups(93%).The average spontaneous bowel movement per week was 9.3% in β-galactosido-sorbitol group when compared to 7.2% in β-galactosido-fructose group. Proportion of patient with their first spontaneous bowel movement after first drug administration with in twenty four hour was 73% in β-galactosido-sorbitol group and 53.33% in β-galactosido-fructose group similarly with in fourty eight hours was 93% in β-galactosido-sorbitol group and 84.44 % in β-galactosido-fructose group. Though the frequency of evacuations was more in β-galactosido-sorbitol group when compared to β-galactosido-fructose group, there was no significance significant difference ($p=0.1079$) in terms of bowel movement produced by both the drugs.

In 75.28% patients in β-galactosido-sorbitol group normal soft consistency stools were formed when compared to 67.05% in β-galactosido-fructose group. The taste and palatability of the drug were found satisfactory in 80.90% patients in β-galactosido-sorbitol group and 48.86 % in β-galactosido-fructose group. The overall patient's response was satisfactory for 80.90% of patients in β-galactosido-sorbitol group compared to 47.73 % in β-galactosido-fructose group.

There were three cases of major adverse effects though not serious in nature in the study period. Two in β-galactosido-fructose group were, severe abdominal pain and severe dehydration and one in β-galactosido-sorbitol group was watery stools. These three patients stopped medication. There were also increased frequency of minor side effects like pain and straining on defecation, nausea and vomiting, sensation of incomplete evacuation and flatulence in β-galactosido-fructose group. β-galactosido-sorbitol was found to be significantly superior to β-galactosido-fructose in terms of less number of above adverse effects($p=0.0309$)

DISCUSSION

In our present study the spontaneous bowel movements in the study period was found to be more in β-galactosido-sorbitol group 9.302±1.090% in comparison to 7.209 ±0.6857% in β-galactosido-fructose group, but it was not found to be significant. Normal and soft consistency stools were seen in 75.28% patients among β-galactosido-sorbitol group and 67.05% in β-galactosido-fructose group. In a similar study conducted by Hammer and Raveli, 76% pateints with β-galactosido-sorbitol and 67% in the β-galactosido-fructose had normal and soft stool [23]. In our present study β-galactosido-sorbitol was found to be significantly superior to β-galactosido-fructose in less adverse effects ($p<0.05$).The taste and palatability of β-galactosido-sorbitol was found satisfactory in 80.90% in β-galactosido-sorbitol group when compared to 48.86% in β-galactosido-fructose group. In a similar study conducted by Pitzalis et al patient treated with β-galactosido-sorbitol considered better palatable when compared to patients treated with β-galactosido-fructose group. The better palatability of β-galactosido-sorbitol might be due to less sweet [24]. The overall patient response was satisfactory for 80.90% of patients in β-galactosido-sorbitol group and 47.73% in β-galactosido-fructose group. Our results were comparable to results of the similar study conducted by Saccheta et al where overall patient acceptability was 73% in β-galactosido-sorbitol group when compared to 26.8 in β-galactosido-fructose group [25]. Similarly a meta-analysis study conducted by Amit Mayedo had patient acceptability of 73.2% among β-galactosido-sorbitol patients and 26.8% in β-galactosido-fructose group [26]. The decreased acceptance among β-galactosido-fructose group could be due to excessive sweetness leading to nausea and other gastro intestinal side effects. Due to all the above results the patients in β-galactosido-sorbitol group had better compliance when compared patients in β-galactosido-fructose group.

CONCLUSION

According to the results obtained from our study and its comparison with similar studies done earlier, β-galactosido-sorbitol has similar efficacy in spontaneous bowel movements when compared to β-galactosido-fructose, but in addition β-galactosido-sorbitol has increased acceptability and compliance due to its decreased sweetness in comparison β-galactosido-fructose. Also β-galactosido-sorbitol has less adverse effects when compared to β-galactosido-fructose. Hence β-galactosido-sorbitol can be used as an osmotic laxative in behalf of β-galactosido-fructose whenever the later is considered for treatment of constipation.

REFERENCES

[1] Connell AM, Hilton C, Irvine G, Lennard-Jones JE, Misiewicz JJ. Br Med J 1965;2:1095–9.
[2] Drossman DA, Sandler RS, McKee DC, Lovitz AJ. Gastroenterol 1982;83: 529–34.
[3] Leung L ,Riutta T, Kotecha J, Rosser W. JABFM 2011; 24(4):436-51
[4] Sonnenberg A, Koch TR. Dig Dis Sci 1989;34:606-11.
[5] Jacobs T Q, Pamies R J. J Natl Med Assoc 2001; 93(1):22-30
[6] Bingham S A, Cummings J H. Gastroenterol 1989;97:1389-99.
[7] Bonapace E S, Fisher R S. Gastroenterol Clin North Am 1998;27:197-211.
[8] Shafer RB, Prentiss RA, Bond JH. Gastroenterol 1984;86:852-855.
[9] Battle W M, Snape W J, Alavi A, Cohen S, Braunstein S. Gastroenterol 1980; 79:1217-21.
[10] Johanson J F. Med Gen Med 2007;9(2):25
[11] Mann SD, Debinski HS, Kamm MA. Gut 1997;41:675-81.
[12] Tomita R, Tanjoh K, Fujisaki S, Ikeda T, Fukuzawa M. Hepatogastroenterol 2002;49:1540–4.
[13] Towers AL, Burgio KL, Locher JL, Merkel IS, Safaeian M, Wald A. J Am Geriatr Soc 1994;42:701– 6.
[14] Rao SS. Gastroenterol Clin North Am 2003;32:659–683.
[15] Shafik A, Shafik AA, elSibai O, Ahmed I. Med Sci Monitor 2003;9:243–48.
[16] Wahlen K, Finkel R, Panvelil T A. Lippincotts illustrated review Pharmacology.6th edition . Phildelphia: Wolter Kluwers;2012
[17] Satoskar RS, Rege NN, Bhandarkar SD. Pharmacology and pharmacotherapeutics.23rd edition. Mumbai: Popular prakashan;2013
[18] Tripathi K D. Essentials of medical pharmacology.6th edition. New Delhi: Jaypee publication;2008.
[19] Katzubg B G, Masters S B, Trevor A J. Basic and clinical pharmacology.12th edition.Philadelphia:Mac graw hill publication;2012
[20] Trevor AJ, Katzung BG, Hall MK, Masters S B. Pharmacology examination and board review.10th edition. New York:Mc Graww Hill publication;2013.

[21] Bouhnik Y, Neut C, Raskine L, et al. Aliment Pharmacol Ther 2004;19:889–899.
[22] Lederle FA, Busch DL, Mattox KM, et al. Am J Med 1990;89:597–601.
[23] Patil DH, Westaby D, Mahida YR, Palmer KR, Rees R, Clark ML et al. Gut 1987; 28: 255-59.
[24] Pitzalis G, Deganello F, Mariani P, Chiarini-Testa MB, Virgilii F, Gasparri R, et al. Pediatr Med Chir 1995; 17: 223-26.
[25] Maydeo A. J Indian Med Assoc 2010; 108(11): 789-92.