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CLINICAL EFFICACY AND SAFETY OF LACTITOL VERSUS LACTULOSE IN THE TREATMENT OF CONSTIPATION

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ABSTRACT

Background: Constipation is a chronic problem occurring in all age groups, seen regularly by doctors of most specialties. Recently, lactitol - an osmotic laxative similar to lactulose, has been actively promoted and received acceptance in the treatment of constipation. It has been shown to have the advantage of being better tolerated and producing more predictable catharsis as compared to lactulose. **Study design:** An open label, active control, parallel study carried out in 90 patients. At the follow-up visits, the patients' responses to the study drug were recorded in a structured form. Episodes of spontaneous bowel movement, side effects, palatability and patient's acceptability were recorded for a period of seven days of treatment. **Results:** The number of bowel evacuations per week was 9.30 ± 1.09 in lactitol group versus 7.20 ± 0.68 in lactulose group, though not significant difference ($p > 0.05$). Lactitol was found to be significantly superior to lactulose in terms of less number of adverse reactions ($p < 0.05$). The patients inferred lactitol to have better response, found it to be more palatable and had better compliance as compared to lactulose group. **Conclusion:** We conclude that lactitol is as effective as lactulose with significantly lesser side effect profile and superior patient's satisfaction in treatment of constipation.

INTRODUCTION

Constipation is a symptom, not a disease and almost everyone experiences it at some point in their life with poor diet typically being the cause.¹ Epidemiologic data on incidence of constipation vary considerably as a result of differences among diagnostic criteria, definition, dietary and cultural characteristics, subjectivity of self reports and patient population.² Depending on these factors, constipation surveys show prevalence between 1% and more than 20% in the western population. In studies of the elderly population, up to 20% of community dwelling individuals and 50% of institutionalized elderly persons reported symptoms.³ Though there are no exact prevalence studies conducted in India, a literature review mentions the incidence of constipation to be around 15% in India.⁴ The incidence of constipation increases with age, and women are more likely to report constipation than men. This fact is particularly relevant when considering the additional risk of constipation in pregnant women with a prevalence as high as 11-38%.⁵

Definition: Though constipation is a chronic problem in many patients all over the world, the terminology associated with constipation is problematic. The word constipation has several meanings and the way it is used may differ not only between patients but also among different cultures and regions.³ As per the Rome III Criteria; there is constipation if patients who do not take laxatives, fulfill the following two or more criteria with at least 25% of defecations for at least 3 months prior to baseline visit: Straining during defecations, Lumpy or hard stools, Sensation of incomplete evacuation, Sensation of anorectal obstruction/blockage, Manual maneuvers to facilitate defecations (e.g., digital evacuation, support of the pelvic floor) and Fewer than three defecations per week.⁶

Causes: Some of the common causes of constipation are inadequate fibre intake, dehydration due to low fluid intake, lack of physical activity (especially in elderly), medications, irritable bowel syndrome, changes in life or routine such as pregnancy, aging and travel, abuse of laxatives, ignoring the urge to have a bowel movement, colonic inertia, intestinal myopathy, slow transit constipation, specific diseases or conditions such as stroke, diabetes, spinal cord injury, Parkinson's disease and multiple sclerosis. **Risk factors:** Some of the common risk factors for constipation are inadequate diet (fluid or fiber), age >55 years, pregnancy, limited mobility, medications (polypharmacy) especially in the elderly, depression, low income and lower education level, physical and sexual abuse, female gender (higher reporting), recent abdominal or perianal/pelvic surgery, laxative abuse, travel and terminal care patients.

Treatment: The cleansing therapy of alimentary canal as mentioned in Ayurveda has many formulae/ herbs used as laxatives, which were described more than 5000 years ago. “Feeling irregular” might have been a common question in ancient Egypt, since laxatives appear to have dominated their medicinal use, with bulk laxatives such as figs, bran and dates in common use. Since then we have come a long way in use of different laxatives according to their mode of action. There is however some degree of overlap between different groups and in some cases the exact mechanisms of action are not known clearly. Many traditionally used laxatives have fallen from use, owing to the violence of their action or their adverse effect profile. Of late, osmotic laxatives are widely used throughout all age groups commonly for their precise and effective action. Osmotic laxatives act by increasing intestinal osmotic pressure thereby promoting fluid retention within the bowel. The drugs used under this class are magnesium and sodium salts, glycerol, lactulose and lactitol. Lactulose (β -galactosido-fructose) has been used since 1966 for hepatic encephalopathy⁷ and is now widely accepted and used as the drug of choice for treatment of constipation. It is a synthetic non-digestible sugar disaccharide containing β -galactose and fructose.

Lactitol (β -galactosido-sorbitol), a disaccharide analogue of lactulose has also been described and used as a laxative.⁸ This compound is easily produced from lactose in a chemically pure form and can be dispensed as both powder and syrup form. It is similar to lactulose in that it is neither broken down nor absorbed in the small intestine, but is extensively metabolized by colonic bacteria. It would seem the ideal replacement to lactulose for treatment of both constipation and hepatic encephalopathy due to its better safety profile and patients acceptability.

MATERIALS AND METHODS

Study design: This was an open label, parallel design and active comparative study, conducted amongst 90 patients aged 18 years and above with a history of constipation. 45 patients in lactitol (Exitol) group and 45 patients in lactulose group randomly.

Inclusion criteria: Men and non-pregnant women above 18 years of age fulfilling the Rome III diagnostic criteria for constipation were included in the study.

Exclusion criteria: Patients with severe renal or hepatic insufficiency, suspected or known cancers, anal abscess, fissure, rectocele, Irritable Bowel Syndrome (IBS) and gastrointestinal obstructions were excluded from the study. Similarly, pregnant or lactating women and patients with cardiac conditions were excluded from the study.

Study procedure: 45 patients each with a history of constipation were enrolled in either the lactitol or lactulose group. After detailed history and clinical examination, patients were enrolled in either of the study groups after fulfilling the above study criteria. Each patient was given a free sample bottle of either lactitol or lactulose with instructions on dosage and duration. All patients were advised to consume 15 ml/day orally as a single dose for first three days, and an increased dose of 30 ml per day orally as a single dose for next four days. Dose was to be taken after night meal or just before going to bed for seven consecutive days.

Follow-up and assessment: All patients in both the study groups were instructed to attend the clinic on day 4 and on day 8 for clinical evaluation. At these follow-up visits, the patients' responses to the study drug were recorded in a structured form for both the study groups. They were enquired about the Spontaneous Bowel Movement (SBM) count or number of stools passed, SBM (stools passed) within 24 hours and 48 hours of first drug administration, frequency of enemas, suppository used or digital evacuations in seven days of treatment. Patients self assessed the taste and palatability of the drug as satisfactory, average or unsatisfactory. They were also enquired for subjective symptomatic relief (pain and straining during defecation, belching/flatulence, feeling of fullness in stomach, consistency of stools, abdominal distention and sensation of incomplete evacuation). The overall patient's response to the drug was assessed as satisfactory, average or unsatisfactory.

Study end points: Primary end point was the proportion of patients with SBM count of 3 or more at the end of 7 days known as complete response to treatment without using any other laxatives during this period. The secondary end point was proportion of patients with a SBM within 24 hours and 48 hours of first drug administration and the drug's safety profile. Safety and tolerability assessment were carried out throughout 7 days of study period.

RESULTS AND OBSERVATIONS

Statistical Analysis: This was carried out with help of software Graph pad prism (version 5) to find out significant differences between the two laxatives. We analyzed the study data for Spontaneous Bowel Movement (efficacy) and incidence of adverse events (safety profile in both the study groups) using unpaired students t-test. The treatment difference were considered significant at $p < 0.05$.

Spontaneous Bowel Movement: The proportion of patients having a SBM count of 3 or more at the end of 7 days having a complete response to treatment was found to be equal in both the study groups (93%). The average SBM per week was 9.3 in lactitol group versus 7.2

in lactulose group. Proportion of patients with their first SBM after first drug administration within 24 hours was 73% in lactitol group versus 53.33% of patients in lactulose group and within 48 hours was 93% in lactitol group and 84.44% of patients in lactulose group. Though the frequency of evacuations were more in lactitol group compared to lactulose group, we found that there was no significant difference ($p = 0.1079$) in terms of bowel movement produced by produced by both the drugs (Table 1).

<i>Table 1 — Summary of Results</i>		
Parameters	Lactitol	Lactulose
Spontaneous Bowel Movement/week	9.302 ± 1.090	7.209 ± 0.6857
Incidence of adverse reactions	$27.16 \pm 3.923\%$	$42.93 \pm 5.122\%$
Consistency of stools (normal/soft)	75.28%	67.05%
Satisfactory taste and palatability of drug	80.90%	48.86%
Overall patient's acceptability of drug	80.90%	47.73%

Normal/soft consistency stools were seen in 75.28% patients of lactitol group compared to 67.05% in lactulose group. Taste and the palatability of drug were found satisfactory by 80.90% of patients in lactitol group compared to 48.86% in lactulose group. A significant proportion of patients treated with lactitol found it to be more palatable and had better patient compliance as compared to patients treated with lactulose. The overall patient's response was satisfactory for 80.90% of patients in lactitol group compared to 47.73% in lactulose group.

Incidence of adverse events: There were 3 cases of major adverse reactions though not serious in nature, two in lactulose group and one in lactitol group. In lactulose group, one patient had severe abdominal pain with weakness and the other had severe dehydration with weakness. Both these patients stopped treatment after three days of taking medication. In lactitol group, one patient stopped medication by third day due to watery stools. There were higher frequency of minor adverse effects like pain and straining on defecation, nausea and vomiting sensation due to excessive sweetness, sensation of incomplete evacuation and flatulence in lactulose group compared to lactitol group. Lactitol was found to be significantly superior to lactulose in terms of less number of above adverse reactions ($p=0.0309$, Table 1).

DISCUSSION

Constipation has become a common problem, both in hospitalized and community dwelling population. Though the definition of normal bowel function varies, it has been suggested that normal defecation frequency is between three times a days to three times per week.⁹ In this current study, Lactitol was found to be at par with lactulose in terms of SBM as there was no significant difference ($p > 0.05$). Normal/Soft consistency stools were seen in 75.28% patients of lactitol group compared to 67.05% in lactulose group in our study. As per *Hammer and Ravelli*¹⁰ study 76% of patients with lactitol reported normal or soft stools compared to 67 % patients with lactulose and similarly in *Doffoel et al*¹⁰ study it was 85% and 83% with lactitol and lactulose respectively. Our results were found to be comparable with the previous comparative studies of lactitol and lactulose with respect to normal/soft consistency of stools. Lactitol was found to be significantly superior to lactulose in terms of less number of adverse reactions ($p < 0.05$) in this study. In the *Hammer and Ravelli*¹⁰ comparative trial, adverse events were observed in 32% patients treated with lactitol compared to 61% patients with lactulose ($p < 0.05$) and similarly a meta analysis conducted by *Amit Maydeo*¹⁰ in constipation had reported incidence of adverse reaction of 31.20 ± 0.800 versus $62.10 \pm 1.100\%$, $p = 0.0019$ with lactitol and lactulose respectively. The significant difference in adverse reaction profile between lactitol and lactulose seen in our study are similar to published literature. Taste and the palatability of drug were found satisfactory by 80.90% of patients in lactitol group compared to 48.86% in lactulose group. Our study results were found to be similar to the previous study by *Pitzalis et al*¹¹, where patients treated with lactitol found it to be more palatable and had better compliance compared to lactulose. A study by *Lanthier et al*⁷ had stated that the reasons for greater acceptability of lactitol over lactulose were its more predictable cathartic effect, convenient once a day dose formulation and preference of its less sweet taste.

The overall patient's response was satisfactory for 80.90% of patients in lactitol group and in lactulose group 47.73%. This was comparable to the study by *Sacchetta et al*¹⁰ with an overall patient's acceptability of 73 % in lactitol group and 26.8 % in lactulose group. A meta-analysis study by *Amit Maydeo*¹⁰ shows patients acceptability for lactitol was 73.2 % compared to 26.8% in lactulose group. The low acceptance of lactulose could be due to its excessive sweetness leading to nausea and gastro-intestinal side effects like meteorism and flatulence.¹² Several clinical trials have shown that lactitol consumption does not increase

blood glucose or insulin levels. The FDA allows the use of a self determined value of 2 kcal/g for lactitol. As sugars normally have 4 kcal/g, the net energy contribution of lactitol is therefore only 50%.¹³ This could be advantageous for treating constipation in diabetic patients. Based on the above facts and studies published lactitol could be the ideal successor to lactulose in treatment of constipation.

CONCLUSION

In view of the results of current study and review of previous literature, we conclude lactitol to be the ideal drug in the treatment of constipation, as lactitol offers efficacy comparable to lactulose with lesser adverse effects and patient's satisfaction superior to lactulose.

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