

## Comparison of Polyethylene Glycol (Peg 3350) and Lactulose in Functional Constipation in Children (1- 4 Years): A Double Blinded- Randomised Controlled Trial

Hitender Rao<sup>1</sup>, Sanjay Mandot<sup>2</sup>, Dileep Goyal<sup>3</sup>, Anjali Vyas<sup>4</sup>

<sup>1</sup>Assistant Professor, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India

<sup>2</sup>Professor and unit head, Department of Pediatrics, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India

<sup>3</sup>Associate Professor, Department of Pediatrics, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India

<sup>4</sup>Resident, Department of Pediatrics, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India

Received: 18-10-2023 / Revised: 21-11-2023 / Accepted: 26-12-2023

Corresponding author: Dr. Hitender Singh Rao

Conflict of interest: Nil

### Abstract:

**Introduction:** Functional constipation is a common problem confronted by Paediatricians in today's time. It is important for the child's physical and mental health that an early evaluation with prompt treatment is given. The objective of the study was to compare the efficacy of polyethylene glycol 3350 versus lactulose in treatment of functional constipation in children from age 1-4 years.

**Aims:** To compare the safety and efficacy of polyethylene glycol 3350 (PEG) and lactulose for the treatment of functional constipation in children (1-4years)

### Objective:

- To compare the effectiveness of polyethylene glycol and lactulose in the treatment of functional constipation in children
- To compare the short term (up to 12 weeks) adverse effects of both the drugs in the treatment of functional constipation in children

**Methods:** A randomized controlled trial was conducted in Pediatric department, at a tertiary care hospital, Udaipur, Rajasthan, over a period of February 2021-July2022, after obtaining permission from ethical committee of the institute. Total 70 children (age 1-4years) with functional constipation according to Rome IV criteria were included in the study.

Polyethylene glycol 3350 was given in one group while lactulose was given to another group. Improvement in number and consistency of stools according to Bristol scale at 4, 8 and 12 weeks was considered as primary outcome and adverse events were the measure of secondary outcome.

**Results:** Among 70 children, with 35 children in each group, results by 12<sup>th</sup> week in PEG 3350 group showed 8.6 to be mean number of stools per week and lactulose group showed 7.1. PEG3350 group showed statistically significant difference when compared to lactulose group (P value = 0.0001). At 12 weeks, PEG 3350 group showed 4.5 to be the mean stool consistency (Bristol scale) per week and lactulose group showed 3.9 per week with a statistically significant on comparison (P value = 0.038). Common side effects observed in both groups were bloating and abdominal pain.

**Conclusion:** Polyethylene glycol 3350 is a safer and more effective alternative to lactulose in the treatment of functional constipation in children. Both PEG 3350 and lactulose were successful in treatment, although the PEG 3350 group significantly showed more efficacy and low and mild overall rates of adverse events.

**Keyword:** Functional constipation, Bristol scale, Rome IV criteria.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

### Introduction

Functional constipation in children is a leading health problem in today's world. It is a symptom and not a disease. Functional constipation is often an underestimated problem leading to decrease in quality of life of both children and parents. Every

patient experiences different clinical features which make them fall under the criteria of functional constipation. Functional gastrointestinal disorders (FGIDs) classification and diagnostic criteria began in the late 1980s [1,2]. The Rome criteria have

been evolving from the first set of criteria issued given in 1989 (The Rome Guidelines for IBS) through the Rome Classification System for functional gastrointestinal disorders (1990), or Rome-1; the Rome I Criteria for IBS (1992) and the functional gastrointestinal disorders (1994), the Rome II Criteria for IBS (1999) and the functional gastrointestinal disorders (1999) to the Rome III Criteria (2006)[3,4]. In May 2016, Rome IV updated the definition of functional constipation which included 33 adult and 20 pediatric FGIDs[5].

**Rome IV criteria for Infants Up to 4 Years**[6]. Must include 1 month of at least 2 of the following:

1. Two or fewer defecations per week
2. History of excessive stool retention
3. History of painful or hard bowel movements
4. History of large-diameter stools
5. Presence of a large fecal mass in the rectum

In toilet-trained children, the following additional criteria may be used:

1. At least 1 episode/week of incontinence after the acquisition of toileting skills
2. History of large-diameter stools that may obstruct the toilet

The prevalence of functional constipation in childhood varies from 0.7% to 29.6%. It comprises of 3% general pediatric outdoor visits and around 30% of pediatric gastroenterology visits. [7-9]. Study done by Shipra Sharma, et al; in children from 2 months to 14 years of age in Raipur found the incidence of functional constipation to be 86.4%[10]. Sumanth Reddy Musali, et al; found 17% prevalence of functional constipation among the children of age group 1 to 14 years [11].

Constipation is broadly divided into two types-Organic and Functional. Common organic causes are- Hirschsprung's disease, cow milk protein allergy etc [12]. Functional constipation is a form of constipation in children with symptoms and no anatomic, physiologic or histopathological abnormality to explain the same.

Causes of functional constipation are low fiber diet, very less water intake/dehydration, milk rich diet, lack of toilet training, change in environment e.g., change in school, preschool children do not want to interrupt playtime, fear of defecation due to previous hard and painful stool causing habitual constipation.

Common age group is toddlers and preschool children, shortly after toilet training. It is more common in boys than in girls. Atypical history given by patients is presence of hard stools—often pellet like/goat stool like, painful bowel movement, h/o fear of defecation, h/o fecal soiling, multiple doctor consults, intermittent use of laxatives and not toilet trained. Management of functional

constipation includes various methods such as education/parent counseling. It should be done about the cause of constipation and need for long term laxative treatment, toilet training should be done for every child only after 24 months of age, consumption of high fiber intake, adequate intake of water or any fluids, restrict consumption of dairy products, disimpaction—use of laxative. Two main drugs used in the treatment of functional constipation in children are: polyethylene glycol & lactulose.

Efficacy and safety profile comparing polyethylene glycol 4000 and lactulose have been studied but mostly in adult population and children of different age group. However, literature pertaining to the use of PEG 3350 in functional constipation in children is limited and there is lack of double blinded randomized controlled trials. Despite some studies showing polyethylene glycol 3350 with a favorable pharmacokinetic and safety profile, use of polyethylene glycol 3350 as a first-line drug for functional constipation in children is not well accepted. The primary objective of this study is to assess the effectiveness of polyethylene glycol 3350 and lactulose as a first-line treatment for functional constipation.

## Methods

This was a double blinded randomized controlled trial, conducted in Pediatric department at a tertiary care hospital, Udaipur, Rajasthan, over a period of 1.5 years (FEBRUARY 2021-JULY 2022), after obtaining permission from ethical committee of the institute. Children (age 1-4 years) with functional constipation were included in the study. Functional constipation was clinically defined according to ROME IV criteria.

Patients were randomized into two groups by using chit method for a comparable distribution in each group. One group received PEG 3350 and the other group received lactulose. The syrups were stored in identical bottles and placed in Pediatric department. Parents were advised how to administer the drugs at the time of enrolment.

They were also instructed on how to fill the patient's diary and how to perform daily defecation training, for children who were able to consciously control bowel movements. The following variables were reported in the diary: the number of bowel movements, painful defecations, stool consistency according to the Bristol scale, fecal incontinence, and presence of adverse events like abdominal pain, diarrhea, nausea and vomiting, bloating and anal irritation. Patients were asked to come for hospital follow up at 4, 8 and 12 weeks.

Group 1: PEG 3350: 2ml/kg in two divided doses (25ml=13.15gms) Group 2: Lactulose: 2ml/kg in two divided doses (15ml=10gms)

Informed consent was obtained from the parents on pre structured proforma as soon as possible after assessing for eligibility.

The study was approved by the Institutional Research Ethics Board of Geetanjali Medical College and Hospital (GMCH), Udaipur (Ref: GU/HREC/EC/2021/1802). The sample size required for this study was 70 (35 in each group) which was decided on the basis of incidences in the previous studies.

**Statistical analysis:** The collected data was transformed into variables, coded and entered in

Microsoft Excel. Data was analyzed and statistically evaluated using SPSS-PC-20 version.

Quantitative data was expressed in mean, standard deviation and difference between two comparable groups was by student's t-test (unpaired) while quantitative data was expressed in percentage.

Statistical differences between the proportions were tested by chi square or Fisher's exact test. P value less than 0.05 was considered statistically significant.

## Results

**Table 1: Descriptive analysis of clinical symptoms in the study population (n=70)**

Clinical symptoms	Frequency	Percentages
Large Volume of Stool	65	92.2%
Hard Stool	65	92.2%
Painful Defecation	63	90.6%
Retention Of Stool	50	72%
Abdominal Pain	43	61.1%
Fecal Incontinence	23	32.8%
Urinary incontinence	14	20.2%

Large volume of stools were complained in 65 children (92.2%) and hard stools also in 65 children (92.2%), followed by painful defecation as the second most common clinical symptom found in 63 (90.6%) children. Other symptoms found were retention of stools (72%), abdominal pain (61.1%), fecal incontinence (32.8%) and urinary incontinence (20.2%).

**Table 2: Descriptive analysis of number of stools per week on follow up weeks after starting treatment**

	4 <sup>th</sup> week		8 <sup>th</sup> week		12 <sup>th</sup> week	
	Mean	P value	Mean	P value	Mean	P value
PEG3350	6.7	0.047	7.2	0.001	8.6	0.0001
Lactulose	5.9		5.9		7.1	

Among the study population, in PEG group, the mean number of stools per week at 4<sup>th</sup> week was 6.7, it was 7.2 at 8<sup>th</sup> week and 8.6 at 12<sup>th</sup> week and in lactulose group, the mean number of stools per week at 4<sup>th</sup> week was 5.9, it was 5.9 at 8<sup>th</sup> week, and 7.1 at 12<sup>th</sup> week. Outcome of number of stools were observed in both the group and PEG 3350 showed statistically significant difference (P value = 0.0001) at 12 weeks.

**Table 3: Descriptive analysis of stool consistency (Bristol scale) per week on Follow up after starting treatment**

	4 <sup>th</sup> week		8 <sup>th</sup> week		12 <sup>th</sup> week	
	Mean	P value	Mean	P value	Mean	P value
PEG3350	3.9	0.277	4.2	0.021	4.5	0.038
Lactulose	3.7		3.7		3.9	

Among the study population, in PEG group, the mean stools consistency per week according to Bristol scale at 4<sup>th</sup> week was 3.9, it was 4.2 at 8<sup>th</sup> week, and 4.5 at 12<sup>th</sup> week and in lactulose group, the mean stools consistency per week at 4<sup>th</sup> week was 3.7, it was 3.7 at 8<sup>th</sup> week, and 3.9 at 12<sup>th</sup> week. Outcome of stools consistency per week were observed in both the group and PEG 3350 showed significant difference (P value = 0.038) at 12 weeks.

**Table 4:**

Side effects	PEG3350			Lactulose			Pvalue		
	4th week	8th week	12th week	4th week	8th week	12th week	4th week	8th week	12th week
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)			
Bloating	14(40%)	8(22%)	4(12%)	19(55%)	14(40%)	11(32%)	0.210	0.106	0.044
Abdominal pain	9(26%)	6(17%)	2 (7%)	12(34%)	10(28%)	9(25%)	0.468	0.273	0.041
Anal irritation	8 (22%)	4(11%)	0%	10(29%)	7(21%)	2(7%)	0.504	0.257	0.113
Diarrhea	4(10%)	1(4%)	0%	2(7%)	2(7%)	1(3%)	0.655	0.584	0.305
Nausea/vomiting	1 (3%)	1 (3%)	0%	2 (7%)	1 (4%)	0%	0.445	0.821	-

Above table shows various side effects of both PEG3350 and lactulose on follow up at 4<sup>th</sup>, 8<sup>th</sup> and 12<sup>th</sup> week. Significant improvement in PEG3350 group in bloating was seen at 12<sup>th</sup> week with P value of 0.044. Similarly, significant improvement in PEG 3350 group in abdominal pain was seen at 12<sup>th</sup> week with P value of 0.041. Other side effects showed improvement in both the groups equally by the end of 12 weeks.

### Discussion

Constipation is often not viewed as a significant problem by many pediatricians. An early and precise assessment with a prompt treatment is very important for the child's physical and mental well-being along with life style.

In our study the mean number of stools per week at the time of enrolment and before starting the treatment was 1.9 and median was 2.0. Out of which children who were prescribed PEG3350 and lactulose had mean number of stools per week as 1.85 and

1.94. The mean stool consistency according to Bristol scale during enrolment was 1.71 and median was 2.0 out of the total study population. Out of which children who were prescribed PEG3350 had mean stool consistency 1.68 and children who were given lactulose had mean stool consistency according to Bristol scale 1.74. Studies by Jarzebicka D, et al; show similar results of mean 1.9 [13]. Khanna et al; recorded mean of 2.8 stool per week [14]. Similarly, study done by Sumanth Reddy Musali, et al; found 50.6% of children were passing <3 stools per week [11].

The mean value of the number of stool per week increased at 4<sup>th</sup>, 8<sup>th</sup> and 12<sup>th</sup> week, in which the mean value of the PEG 3350 prescribed children was 6.7 at 4<sup>th</sup> week, 7.2 at 8<sup>th</sup> week and 8.6 at 12<sup>th</sup> week. While lactulose group appeared to show mean number of stools of 5.9 at 4<sup>th</sup> week, 5.9 at 8<sup>th</sup> week and 7.1 at 12<sup>th</sup> week. Therefore, PEG 3350 showed statistically significant difference when compared to lactulose in terms of number of stools per week on follow up (P value = 0.0001). These results come in concordance with the study done by Gremse DA et al; in which 37 kids between the ages of 2 and 16 were treated for constipation using unblinded, randomized, crossover designs comparing polyethylene glycol (PEG) 3350 with lactulose. Similarly, Jarzebicka D, et al; also found PEG 3350 to have improved number of stools on follow up when compared to children who were given lactulose [13].

The mean stool consistency also showed statistically significant difference when we compared the two drugs (P=0.038) at the end of 12<sup>th</sup> week. Mean value of stool consistency based on Bristol scale at 4<sup>th</sup>, 8<sup>th</sup> and 12<sup>th</sup> week, in which

mean value of the children who received PEG 3350 was 3.9 at 4<sup>th</sup> week, 4.2 at 8<sup>th</sup> week and 4.5 at 12<sup>th</sup> week. While means tool consistency according to Bristol scale for children who received lactulose was 3.7 at 4<sup>th</sup> week, 3.7 at 8<sup>th</sup> week and 3.9 at 12<sup>th</sup> week. Similar results were seen in a study done by Jarzebicka D, et al; among 102 patients comparing the effect of PEG3350 and lactulose in children with functional constipation [13].

While assessing the side effects caused by the drugs in our study, in PEG 3350 and lactulose group, 14 (40%) and 19 (55%) of them had bloating (P value=0.210), 9 (26%) and 12 (34%) of them had abdominal pain (P value=0.468), 8 (22%) and 10 (29%) of them had anal irritation (P value=0.504), 4 (10%) and 2 (7%) of them had diarrhea (P value=0.655) and 1 (3%) and 2 (7%) had nausea/vomiting (P value=0.445), at 4<sup>th</sup> week. Side effects further improved in PEG 3350 and lactulose group, 4 (12%) and 11 (32%) of them had bloating (P value=0.044), 2 (7%) and 9 (25%) of them had abdominal pain (P value=0.041), 0 and 2 (7%) of them had anal irritation (P value=0.113), 0 and 1 (3%) of them had diarrhea (P value=0.305) and 0 had nausea/vomiting at 12<sup>th</sup> week. Similar side effects were seen in study done by Jarzebicka D, et where bloating and abdominal pain were commonly found [13].

Although there is no major difference in the proportion of side effects according to our study, we observed that bloating and abdominal pain was the most common side effect. In addition to dietary adjustments and behavioral modification, laxatives are advised for the treatment of chronic constipation in children. The limitation of our study was that we could have had wide spectrum and enrolled children of age more than 4 years. The sample size of our study was also small for the outcomes related to various adverse effects.

### Conclusion

We concluded that polyethylene glycol 3350 is a safer and more effective alternative to lactulose in the treatment of functional constipation in children. Both PEG 3350 and lactulose were successful in the treatment, although the PEG3350 group significantly showed more efficacy. The results support the overall conclusion that PEG 3350 is comparable in its efficacy to lactulose for treating functional constipation. The overall rates of adverse events are low and mild in severity, suggesting a fairly safe profile for PEG 3350 in an actual clinical context.

### References

1. Torsoli A, Corazziari E. The WTR's, the delphic oracle and Roman conclaves. *Gastroenterol Int.* 1991; 4:44-45.
2. Milholland AV, Wheeler SG, Heieck JJ.

- Medical assessment by Adelphi group opinion technic. *N Engl J Med.* 1973; 298:1272–1275.
3. Thompson, WG, Dotevall, G, Drossman, DA, Heaton, KW, and Kruis, W. Irritable bowel syndrome: guidelines for the diagnosis. *Gastroenterol Int.* 1989;92-95.
  4. Drossman, DA, and the Rome IV Committees. Rome IV functional gastrointestinal disorders: disorders of gut-brain interaction, Drossman, DA, Chang, LC, Kellow, WJ, Tack, J, and Whitehead, WE, ed. Raleigh, NC: The Rome Foundation, 2016; 549-576.
  5. Drossman, DA, Thompson, WG, et al. Identification of subgroups of functional bowel disorders. *Gastroenterol Int.* 1990; 3: 159-172.
  6. AzizI, Whitehead WE, Palsson OS, et al. An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. *Expert Rev Gastroenterol Hepatol.* 2020 Jan; 14(1):39-46.
  7. Liem O, Harman J, Benninga M. Health utilization and cost impact of childhood constipation in the United States. *J Pediatr* 2009; 154:258-262.
  8. Croffie JM. Constipation in Children. *Indian J Pediatr.* 2006; 73:697-701.
  9. Partin JC, Hamill SK, Fischel JE, Partin JS. Painful defecation and fecal soiling in children. *Pediatrics.* 1992; 89: 1007 -1009.
  10. Shipra Sharma, Sukhlal Nirala, Rajendra Ratre. Clinico-etiological spectrum of constipation in children. *International Surgery Journal. Int Surg J.* 2019 Nov;6(11):3996-4000.
  11. Musali SR, Damireddy AR. Prevalence and profile of functional constipation among children aged 1–12 years at a tertiary care center. *MRIMS J Health Sci.* 2023 Jan 13.
  12. Swenson O. Hirschsprung's disease: a review. *Rev Pediatr.* 2002; 109:914–918.
  13. Jarzebicka D, Sieczkowska - Golub J, Kierkus J, et al. PEG 3350 versus lactulose for treatment of functional constipation in children: randomized study. *Journal of Pediatric Gastroenterology and Nutrition.* 2019 Mar 1; 68(3):318-24.
  14. Vikrant Khanna, et al. Etiology and Clinical Spectrum of Constipation in Indian Children. *Indian Pediatrics.* 2010; 47: 1025-1030.