

**PROTOCOL OF THESIS FOR THE PARTIAL FULFILLMENT OF
MS DEGREE IN GENERAL SURGERY**



**“Efficacy of Polyethelene Glycol vs Lactulose with Isabgol in Acute fissure-in-Ano:
A Randomized Control Trial. (PEGASIS trial)”**

All India Institute of Medical Sciences
Bhubaneswar – 751019

Candidate:

Dr. Aitha Saikrishna

Academic Junior Resident.

Department of General Surgery.

saisurya.aitha@gmail.com

8919330687

Chief guide:

Dr. Prakash Kumar Sasmal

Additional Professor

Department of General Surgery

drpksasmal@gmail.com

9438884255

Co-guide:

Dr. Pankaj Kumar

Associate Professor

Department of General Surgery

9711090814

Consent of Guide, Co-guide and Head of Department

Title of thesis:

**“Efficacy of Poly Ethelene Glycol vs Lactulose with Isabgol in Acute fissure-in-Ano:
A Randomized Control Trial. (PEGASIS trial)”**



Signature of the Candidate

Signature of Guide

Signature of Co-Guide

Signature of HOD

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IEC FORMAT FOR POSTGRADUATE THESIS PROTOCOL

1. Full Title of Study:	Efficacy of Polyethelene Glycol vs Lactulose with Isabgol in Acute Fissure-in-Ano: A Randomized Control Trial. (PEGASIS trial)
2.1 Name & signatures of the candidate 2.2 Department 2.3 Degree/course 2.4 Batch of admission to the course 2.5 Month & year of submission of thesis	Dr Aitha Saikrishna Signature _____ General Surgery MS July 2021 Dec 2023
3. Name of Faculty & Department (Chief-Guide/Co-guide)	Signatures (Chief-Guide/Co-Guides)

<p>a. Dr. Prakash Kumar Sasmal Additional Professor Department of General Surgery</p> <p>b. Dr. Pankaj Kumar Associate professor Department of General Surgery</p>	<p>3.1 _____</p> <p>3.2 _____</p>
<p>4. Objectives of the study</p>	<p>Primary objective</p> <ul style="list-style-type: none"> • Time taken for the resolution of acute pain following fissure in ano. Pain will be measured by improvement in visual analog scale (VAS) pain score. Scores will be recorded by making a handwritten mark on a 10-cm line that represents a continuum between "no pain" (score of 0) and "worst pain" (score of 10). <p>Secondary objectives</p> <ul style="list-style-type: none"> • Improvement in constipation assessed by Bristol stool form scale. Acute constipation is the cause and result of acute fissure-in-ano. Stool softeners help in

	<p>alleviating the pain by improving the stool forms assessed by Bristol stool scale. Type 1-2 indicates constipation that exacerbates the pain in an acute fissure in ano. Type 3-4 are ideal stools and easier to pass and Type 5-7 are soft to liquid stools that will be much helpful in alleviating the pain in an acute fissure in ano.</p> <ul style="list-style-type: none"> • Adverse effects any of PEG or lactulose with isabgol. Long term use of PEG or lactulose can result in electrolyte imbalance, diarrhoea, or stomach cramps. Incidence of adverse effects if any will be recorded and reported. • Patient tolerance and compliance to the medications The tolerance and compliance of the drugs will be recorded at the end of one month by personal interviews.
<p>5. Why this study is required? Please provide a brief justification.</p>	<ul style="list-style-type: none"> • The existing literature stresses upon the better efficacy of PEG over other stool softeners like lactulose or isabgol for functional constipation.(1,2) • And there is no consensus regarding PEG vs lactulose combined with isabgol as stool softeners, which we frequently use for treating acute fissure in ano.

	<ul style="list-style-type: none"> Hence a good quality RCT is the need of the hour.
<p>6. Methodology</p>	<p>6.1. Study Design: Randomized Control Trial</p> <p>6.2. Study Setting: Outpatient department, Department of General Surgery, All India Institute of Medical Sciences, Bhubaneswar.</p> <p>6.3. Study Groups: 2 Groups</p> <p>6.4. Sample size: Sample size is a total of 144, 72 in each group which is calculated using Kelsey Fleiss corrected formula in the openepi.com.</p> <p>6.5. Inclusion criteria</p> <ul style="list-style-type: none"> All patients presenting with acute fissure in ano between the age group of 18 to 75 years. <p>6.6 Exclusion criteria</p> <ul style="list-style-type: none"> Pregnancy / lactation Patients not giving consent Patients not able to understand the nature of the study

	<ul style="list-style-type: none">▪ Diabetes mellitus and chronic kidney disease▪ Known intolerance to PEG/Lactulose or Isabgol▪ Prior enrolment in other study.▪ Patient undergoing surgery for Fissure in Ano <p>6.7. Details of Control(s) NA</p> <p>6.8. Details of intervention Administration of Polyethylene glycol in one group, isabgol husk and lactulose in the other group in the recommended dosage to relieve acute constipation. Sphincter relaxants will be also used as local application of Nifedipine with Lignocaine (Anobliss ointment from Samarth Lifesciences Pvt. Ltd., India) in both the groups along with warm water sitz bath.</p> <p>6.9. Duration of study: Two years</p> <p>6.10. Outcome measures:</p> <ul style="list-style-type: none">• Pain will be assessed by VAS score• Presence or absence of bleeding• Stool consistency measured by Bristol stool form scale• Rate of ulcer healing at one month
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	<ul style="list-style-type: none"> • Patient tolerance and compliance to the medications based on TSQM version 1.4 questionnaire. <p>6.11. Investigation specifically related to Protocols: no specific investigation needed</p> <p>6.12. Permission to use copyrighted Questionnaire/proforma: NA</p> <p>6.13. Others: NA</p>
<p>7. Permission from Drug Controller General of India (DCGI)</p>	<p>1. <input type="checkbox"/> Required 2. <input checked="" type="checkbox"/> Not required</p> <p>3. <input type="checkbox"/> Received 4. <input type="checkbox"/> Applied when:</p>
<p>8. Permission from DGFT, if required</p>	<p>1. <input type="checkbox"/> Required 2. <input checked="" type="checkbox"/> Not required</p> <p>3. <input type="checkbox"/> Received 4. <input type="checkbox"/> Applied when:</p>
<p>9. a) Safety measures for proposed interventions</p> <p>b) Results of relevant laboratory tests</p> <p>c) Result of studies in human</p>	<p>a) NA</p> <p>b) NA</p> <p>c) NA</p>
<p>10. Plans to withdraw standard therapy in research</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>

	Remarks: _____
11. Plan for the provision of coverage for medical risk	No specific provision of coverage for medical risk is provided.
12. How you will maintain Confidentiality of the subject?	Confidentiality of the subjects will be ensured and will not be shared before, during, and after the study.
13. Costs Involved (Appx. in Rs.)	Rs 37,000/- for medicines Rs 3000/- for printing of charts and questionnaires
13.1 Investigations	
13.1.1 List of Investigations required in the study which are part of the routine workup	NA
13.1.2 List of Investigations required in the study which are NOT part of routine workup and will be done especially for this research	13.1.2 No specific investigation is required.
13.2 Disposables	13.2 NA

<p>13.3 Implants</p> <p>13.4 Drugs / Contrast Media</p> <p>13.5 Others</p> <p>Who will bear the costs of the requirements which are not part of routine workup? (mark ✓)</p>	<p>13.3 NA</p> <p>13.4 NA</p> <p>13.5 NA</p> <p>1. Chief-guide/co-guides/student <input checked="" type="checkbox"/></p> <p>2. Other Agencies (Name) _____</p>
<p>14. Participant Information Sheet</p> <p>(mark ✓ if yes)</p>	<p>✓ Attached English version</p> <p>✓ Attached Odia version</p> <p>✓ Certified that Odia version is a true translation of English version</p>
<p>15. Participant Informed Consent Form</p> <p>(mark ✓ if yes)</p>	<p>✓ Attached English version</p> <p>✓ Attached Odia version</p> <p>✓ Certified that Odia version is a true translation of English version</p>
<p>16. Whether any work on this Protocol has started or not?</p>	<p><input type="checkbox"/> (mark ✓ if yes, X if no)</p> <p>(Please enclose a separate certificate to this effect).</p>

<p>17.Attached documents</p> <p>(If any)</p>	<p>17.1 Cover letter, through proper channel.</p> <p>17.2 Copy of the detailed Protocol is mandatory (vide Page 6)</p> <p>17.3 Undertaking (vide Page 2)</p> <p>17.4 In case of multi-centric study, IEC clearance of other centers must be provided</p> <p>17.5 Definite undertaking as to who will bear the expenditure of injury related to the Protocol.</p> <p>17.6 In case an insurance cover is intended, Insurance the certificate must be provided (as per ICMR guidelines)</p> <p>17.7 Permission as mentioned in Sl.No. 6,12, 8, 9</p> <p>17.8 In case of Clinical trials, proof of registration of a clinical trial with ICMR needs to be submitted.</p> <p>17.9 Other relevant documents</p>
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THESIS PROTOCOL (MAIN DOCUMENT)

Introduction

Acute fissure in ano is a very common, painful and distressing benign anorectal disorder. It is a linear tear in the anoderm of the distal anal canal most commonly on the posterior midline (3). They usually result from trauma caused by the passage of hard stool and less commonly from diarrhoea also. The most common presenting symptom is pain, bleeding and secondary constipation. Most of the cases are managed conservatively by increased fluid intake, high fibre diet, sitz bath, stool softeners and topical application of sphincter relaxants(4).

Constipation is one of the most common causes of anal fissure. Patients present the outpatient department with acute anal pain which is because of increased internal anal sphincter tone and also hard stool rubbing over the fissure.(3). Acute constipation and pain due to anal fissure is initially managed with lifestyle and dietary modifications like consuming adequate fluids, fibre diet and sitz bath(4).

One of the fibrous supplements is isabgol husk which is a soluble fiber with enormous water absorbing property. Properties like nonirritant to the large bowel, non-fermenting and dichotomous stool normalizing agents make it one of the most preferred bulk-forming agents(5). Low cost and over the counter availability are other plus points. Lactulose is also the most commonly prescribed laxative in anal fissures for constipation. Polyethylene glycol is an osmotic laxative used in the treatment of anal fissures to relieve constipation.

There have been multiple studies that say polyethylene glycol has better efficacy in terms of frequency of stools, and form of stools compared to lactulose or isabgol husk alone. (6) (1)(2). However, there are no studies conducted on the efficacy of Polyethylene glycol vs isabgol husk and Lactulose in Acute fissure in ano. However, studies say that laxatives may reduce/delay the absorption of certain medications, hence medications are advised to be taken 1 hour before or 2-3 hours after taking laxatives.(6).

Patients in both arms are advised Anobliss (lidocaine with nifedipine) ointment for anal canal application to relieve anal spasms and acute pain. Patients in one arm are given polyethylene glycol for 2 weeks maximum and in the other arm, isabgol husk plus lactulose will be given for 2 weeks to improve the Bristol stool score and relieve from acute constipation. Patients will be assessed at 1 week and 1 month and evaluated for primary and secondary outcomes.

Study objectives

Primary objective

- Time taken for the resolution of symptoms

Secondary objectives

- Improvement in Bristol stool score
- Healing of anal fissure at the end of one month
- Adverse effects of PEG and lactulose with isabgol
- Patient tolerance and compliance to the medications

Review of literature

Keywords: Psyllium husk, PEG, Polyethylene glycol, fissure in ano, functional constipation, isabgol, constipation, lactulose Rome IV criteria, Bristol stool scale, laxatives, trials, Anal fissure, vas scale, nifedipine, anobliss.

Search goal: To find studies which describe about efficacy of Polyethylene glycol and isobgol plus lactulose in acute fissure in ano.

Strategy: Searches were made in the databases viz. Pubmed, google scholar, Indmed and various other journals that included Annals of surgery, World journal of surgery, The anatomical record, Surgical clinics of north America, Surgery (United States). The above-mentioned keywords and search goal were used.

Materials and methods

Study setting:

- OPD patients of department of General Surgery, All India Institute of Medical Sciences, Bhubaneswar

Study design:

- Primary purpose – Treatment

Study type:

- Randomised control study

Inclusion criteria:

1. All those having acute fissure in ano between the age group of 18 to 75 yrs

Exclusion criteria:

1. Pregnancy / lactation
2. Patients not giving consent
3. Patients not able to understand the nature of the study
4. Diabetes mellitus and chronic kidney disease
5. Known intolerance to PEG/Lactulose or Isabgol
6. Prior involvement in other study.
7. Patient undergoing surgery for Fissure in Ano

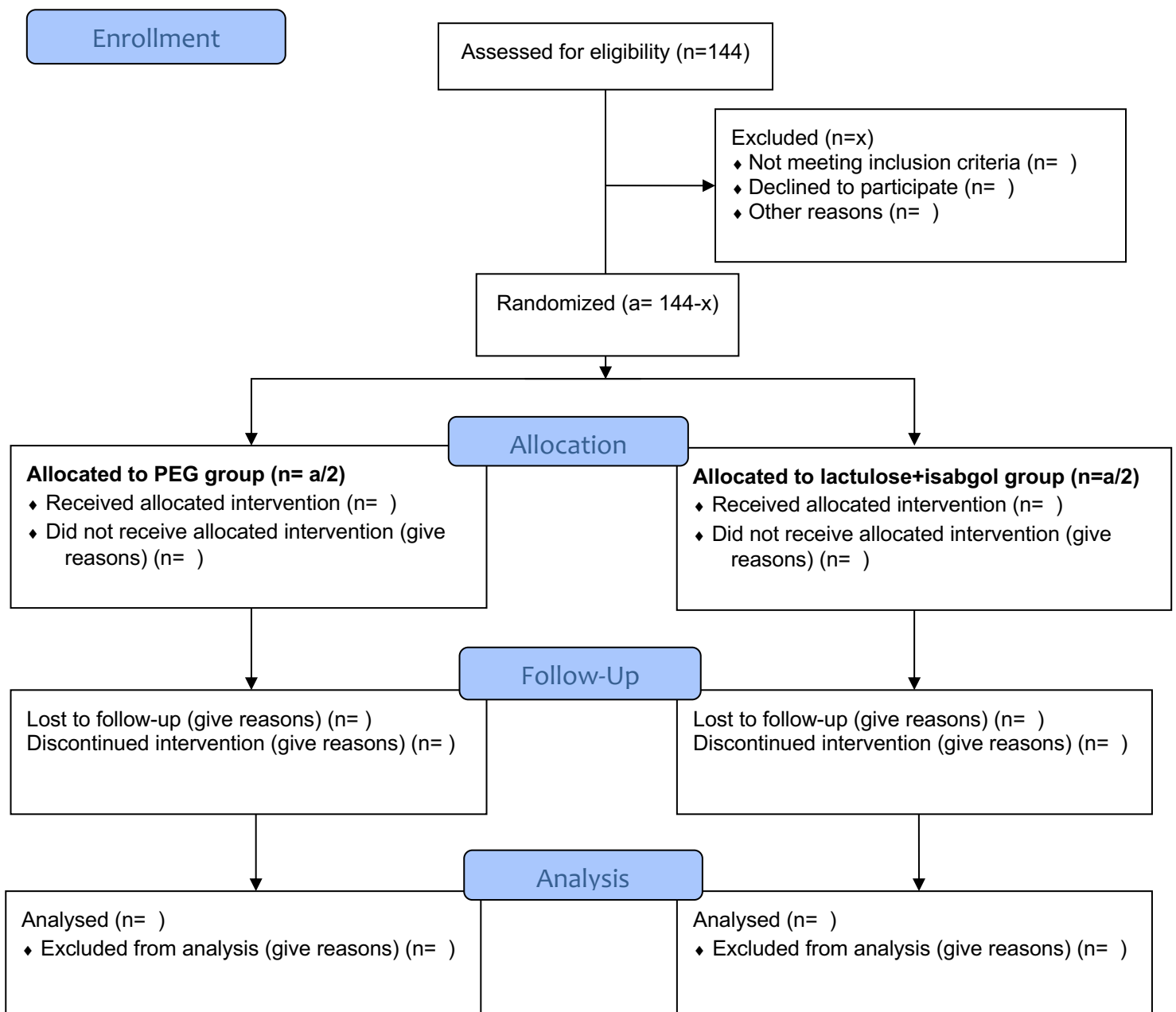
Sample size: Sample size is 144, 72 in each group which is calculated using Kelsey, Fleiss corrected formula in the openepi.com. Based on a previous study on PEG vs isabgol.(2)

Methods:

- **Recruitment:** All patients aged more than 18 years of age presenting to the outpatient department of surgery department AIIMS Bhubaneshwar with complaints of acute fissure in ano will be assessed for recruitment in the study and will be randomly given Polyethylene glycol (PEG) oral solution 15-30 ml once daily up to 2 weeks maximum, or isabgol husk 2 teaspoonfuls in 200 ml of warm water before bedtime plus lactulose syrup 30 ml at bedtime for 2 weeks and assessed for primary and secondary outcomes.
- **Randomization:** Random allocation software
- **Allocation concealment:** Sealed envelope technique

- **Blinding:** Single blinded study (Assessor)
- **Intervention:** PEG and lactulose with isabgol
- **Follow up period:** One week, 1 month

	Pain based on VAS score.	Bristol stool form scale	Healing of fissure	Recurrence.
0 visit			NA	NA
1st visit 1 week			NA	NA
2nd visit 1st month				NA



- Data will be entered in Microsoft excel, and analysis will be done using the latest version of IBM SPSS software.

Ethical issues

- Approval shall be taken from the Ethics Committee of the All India Institute of Medical Sciences, Bhubaneswar.
- Informed written consent will be obtained from patient/patient attenders in their own understandable language.
- A participant information sheet will be provided to the patients.
- Participants will be explained that their identity will remain confidential.

Timelines

ACTIVITY	DEC'21	JAN'22 MAR'22	MAY' 22	AUG'22- JAN'23	FEB'23- JUL'23	SEPT' 23	OCT'23- DEC'23
PROTOCOL SUBMISSION							
ETHICS COMMITTEE							
START OF STUDY							
DATA COLLECTION							
DATA ANALYSIS							
PRESENTATION OF RESULTS							

References

1. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus Polyethylene Glycol for Chronic Constipation. The Cochrane database of systematic reviews [Internet]. 2010 Jul 7 [cited 2021 Dec 31];(7). Available from: <https://pubmed.ncbi.nlm.nih.gov/20614462/>
2. Wang HJ, Liang XM, Yu ZL, Zhou LY, Lin SR, Geraint M. A Randomised, Controlled Comparison of Low-Dose Polyethylene Glycol 3350 plus Electrolytes with Ispaghula Husk in the Treatment of Adults with Chronic Functional Constipation. Clinical drug investigation [Internet]. 2004 [cited 2021 Dec 29];24(10):569–76. Available from: <https://pubmed.ncbi.nlm.nih.gov/17523718/>
3. Beaty JS, Shashidharan M. Anal Fissure. Clinics in Colon and Rectal Surgery [Internet]. 2016 Mar 1 [cited 2021 Dec 28];29(1):30. Available from: [/pmc/articles/PMC4755763/](https://pubmed.ncbi.nlm.nih.gov/2755763/)
4. Nelson RL, Thomas K, Morgan J, Jones A. Non surgical therapy for anal fissure. The Cochrane database of systematic reviews [Internet]. 2012 Feb 15 [cited 2021 Dec 31];2012(2). Available from: <https://pubmed.ncbi.nlm.nih.gov/22336789/>
5. Garg MBBS MASCERS PM. PRACTICE APPLICATIONS Letters to the Editor Psyllium Husk Should Be Taken at a Higher Dose with Sufficient Water to Maximize Its Efficacy. 2017 [cited 2021 Dec 24]; Available from: <http://ees.elsevier.com/andjrnl>
6. Belsey JD, Geraint M, Dixon TA. Systematic review and meta-analysis: polyethylene glycol in adults with non-organic constipation. International journal of clinical practice [Internet]. 2010 Jun [cited 2021 Dec 31];64(7):944–55. Available from: <https://pubmed.ncbi.nlm.nih.gov/20584228/>

7. Psyllium and Alcohol/Food Interactions - Drugs.com [Internet]. [cited 2021 Dec 28]. Available from: <https://www.drugs.com/food-interactions/psyllium.html>