



RESEARCH ARTICLE

EFFICACY AND SAFETY OF LACTULOSE AND POLYETHYLENE GLYCOL (PEG) COMBINATION THERAPY-RELUX L MANUFACTURED BY ESKAG PHARMA PVT. LTD., KOLKATA, INDIA IN THE MANAGEMENT OF CONSTIPATION

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ABSTRACT

Constipation is a prevalent gastrointestinal issue affecting millions worldwide. Polyethylene Glycol (PEG) is commonly prescribed for constipation relief and bowel preparation, with FDA approval for use in individuals aged 17 and older. This article reviews the efficacy and safety of Lactulose in combination with PEG in the management of constipation. PEG, both as a standalone treatment and in combination with Lactulose. PEG is favored for its minimal side effects, improved tolerance, and effectiveness across various patient populations, including adults, pregnant women, and geriatrics. Combination therapy with Lactulose further enhances the efficacy of PEG, offering improved bowel cleansing, reduced side effects, and better patient compliance. Several clinical trials and studies have demonstrated that Lactulose and PEG together provide superior outcomes in terms of stool frequency, consistency, and overall symptom relief. Additionally, a specific product, Relux L, which combines Lactulose and PEG, manufactured by Eskag Pharma Ltd., Kolkata, India, has proven to be an effective option for managing constipation and preparing patients for medical procedures. These findings highlight the role of Lactulose and PEG as key agents in the management of chronic constipation and bowel preparation.

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INTRODUCTION

Constipation is a common gastrointestinal issue that affects millions of people globally. Polyethylene Glycol (PEG) is one of the most frequently used agents for bowel cleansing and constipation relief. The FDA has approved the use of polyethylene glycol (PEG) for the management of constipation in individuals aged 17 and older.(1) PEG is favoured over alternative treatments for chronic constipation and faecal disimpaction due to its minimal adverse effects and more palatable taste. Recent studies have investigated combination effects of PEG with other agents, such as Lactulose, to improve both tolerance and effectiveness. Lactulose and Polyethylene Glycol (PEG) are widely used osmotic laxatives, both demonstrated to be effective and safe in the management of chronic constipation.(2) Their efficacy is primarily evaluated based on outcomes such as increased stool frequency, improved stool consistency, and the alleviation of abdominal discomfort. A 2016 systematic review supports the use of both Lactulose and PEG as first-line therapeutic agents for managing chronic constipation in pregnancy. Furthermore, clinical trials indicate that PEG 4000 significantly enhances

stool frequency and consistency in geriatric patients suffering from chronic constipation.(3) These findings reinforce the role of Lactulose and PEG as key agents in treating various populations affected by chronic constipation, with notable efficacy across age groups and physiological conditions.

Clinical studies

- A placebo-controlled, double-blind, randomized, multicenter trial (N=151) evaluated the efficacy of 17 grams of PEG laxative compared to a dextrose powder placebo, administered daily. The study demonstrated the superiority of PEG, with patients experiencing an average of 4.2 bowel movements versus 2.9 for placebo by the end of week 1 ($P < 0.01$), and 4.5 versus 2.7 by the end of week 2 ($P < 0.001$). PEG was also associated with less cramping, improved stool consistency, and easier passage ($P < 0.001$). No significant differences in laboratory values were observed between the two groups.(4)
- A randomized, placebo-controlled, double-blind, multicenter trial evaluated the efficacy of PEG 3350 over seven days in 203 patients. The results showed that patients in the PEG 3350 group, compared to those receiving placebo, reported a preference for PEG due to

experiencing less stool hardening and reduced exertion during bowel movements ($P < 0.0001$). Additionally, the PEG group reported an improved quality of life, with reductions in pain, bloating, and overall constipation symptoms.(5)

- A double-blind, placebo-controlled, parallel-group study investigated the safety of isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in 70 patients with chronic constipation over six months. Over 20 weeks, the dosage of PMF-100 was progressively reduced, and 77% of patients achieved complete resolution of constipation symptoms compared to 20% in the placebo group. No significant differences in adverse events were observed between the groups.(6)
- In another multicenter, randomized, double-blind, parallel study, PEG 4000 was compared to Lactulose in 96 patients over three months. PEG 4000 demonstrated comparable or superior efficacy and long-term tolerance. Patients in the Lactulose group experienced more vomiting and flatulence. No significant treatment-related differences were found in laboratory values, including electrolytes, total protein, albumin, vitamin A, D, folates, or serum iron.(7)

When combined with PEG, Lactulose further enhances the intestinal cleansing process, increasing the efficacy of PEG and reducing side effects. PEG combined with Lactulose works better for patients with constipation than PEG alone. Lactulose is also palatable and generally well-tolerated by patients, making the combination more acceptable and improving patient compliance (3). Below are some of the studies that have proven the efficacy and better tolerance of the combination therapy with PEG plus Lactulose in patients with constipation. A systematic review of 23 randomized controlled trials evaluated the effectiveness and safety of various laxatives in patients aged 65 and older. Bulk laxatives, osmotic laxatives like polyethylene glycol (PEG), stimulant laxatives, and other medications such as prucalopride, lubiprostone, and elobixibat demonstrated short-term efficacy. The review found polyethylene glycol to be both safe and effective for long-term use, up to six months, among elderly patients with chronic constipation. However, the quality of the included studies was generally low, and most involved small patient samples. A separate study compared the long-term use of PEG 4000 and Lactulose in elderly patients, demonstrating that PEG 4000 had better stool frequency and consistency without causing nutritional deficiencies or significant adverse effects.

Table. Characteristics of studies that evaluated the combination effects of PEG + Lactulose in constipation and proved better efficacy and tolerance [9-20] Clinical studies on PEG 4000 and Lactulose in elderly patients

Study (year)	PEG-Lactulose (n)	PEG (n)	Treatment	Design	With constipation
Zhang ZY et al. (2018)	16	16	PEG 2L+Lactulose 90 mL	Randomised	Yes
Zheng Y et al. (2018)	40	40	PEG 2L+Lactulose 60 mL	Randomised	Yes
Yu ZB et al. (2018)	36	36	PEG 2L+Lactulose 120 mL	Single-blind, randomised	Yes
Nong CS et al. (2015)	36	36	PEG 1L+Lactulose 20 mL	Randomised	Yes
Wu J et al. (2018)	84	91	PEG 3L+Lactulose 180 mL	Randomised	Yes
Zhang XT et al. (2019)	45	45	PEG 4L+Lactulose 60-180mL	Randomised	Yes
Xu HR et al. (2015)	90	90	PEG 0.75L+Lactulose 90 mL	Single-blind, Randomised	Yes
Jiang XL et al (2017)	50	50	PEG 1-2L+Lactulose 90 mL	Single-blind, randomised	Yes
Wang Q et al. (2015)	74	74	PEG 2L+Lactulose 120 mL	Randomised	Yes
Huang RW et al. (2015)	45	45	PEG 2L+Lactulose 60 mL	Randomised	Yes
Wu Y et al. (2016)	53	53	PEG 2L+Lactulose 30 mL	Randomised	Yes
Lu et al. (2016)	45	45	PEG 2L+Lactulose 30 mL	Single-blind, randomised	Yes
Han LX et al. (2016)	35	35	PEG 3L+Lactulose 45 mL	Randomised	Yes

Specific Patient Population

- **Pregnant Women:** PEG is classified as a pregnancy category C medication. Due to minimal systemic absorption, it is unlikely to pose significant risks to neonates. Despite limited research, the American Academy of Family Physicians considers PEG the preferred treatment for chronic constipation in pregnant women.
- **Breastfeeding Women:** No specific recommendations for PEG use in breastfeeding women are provided by the manufacturer. However, given PEG's poor systemic absorption, its presence in breast milk is expected to be clinically insignificant.(8)
- **Geriatric Patients:** No dose adjustment is required for geriatric patients.

The Role of Lactulose in Combination Therapy

Lactulose, a disaccharide, acts as an osmotic laxative when ingested. It passes unabsorbed through the digestive tract and reaches the colon, where it retains water and electrolytes, resulting in a hyperosmotic environment. This not only helps expel toxins and ammonia from the intestines but also relieves constipation symptoms by softening the stool and promoting bowel movements (3).

The study concluded that PEG 4000 is a well-tolerated and more effective treatment than Lactulose for long-term management in older adults (2, 21)

Clinical studies on PEG 4000 and Lactulose in adult patients: In adults, the combination of polyethylene glycol (PEG) and Lactulose has been found to improve bowel preparation quality. A meta-analysis of 18 studies involving 2,274 adult patients showed that PEG combined with Lactulose offers better efficacy than PEG alone, especially in patients with constipation. The combination was associated with cleaner bowel preparation and a higher adenoma detection rate (ADR), essential for effective colonoscopy. The studies also indicated that PEG-Lactulose combinations resulted in fewer adverse reactions like abdominal pain, nausea, and vomiting compared to using PEG alone. Moreover, another study highlighted the superiority of PEG-Lactulose in long-interval preparation-to-colonoscopy, allowing for more flexible scheduling of colonoscopies. This combination approach offers a more effective bowel cleansing strategy, enhancing the overall quality and outcomes of the colonoscopy procedure. (15, 22-23)

Advantages of Lactulose and PEG Combination: Research has shown that the combination of Lactulose and PEG leads to

better results than PEG alone, especially in patients who suffer from constipation. The benefits of this combination include:

- **Enhanced Bowel Preparation:** The osmotic action of Lactulose increases water retention in the intestines, leading to a more thorough cleanse.
- **Reduced Side Effects:** The combination is associated with fewer symptoms of nausea, bloating, and dizziness, which are common with PEG alone.
- **Improved Compliance:** Lactulose's palatability and tolerability make it easier for patients to adhere to the regimen.

Relux L manufactured by Eskag Pharma Ltd., Kolkata, India: One product, Relux L, manufactured by Eskag Pharma Ltd., Kolkata, India, has shown promise by combining both Lactulose and PEG in a liquid form, providing enhanced results for constipation relief and bowel preparation.

Indications for Relux L

Relux L by Eskag Pharma is indicated for:

- **Constipation Relief:** Particularly beneficial for patients suffering from chronic or acute constipation.
- **Bowel Preparation Before Colonoscopy or Surgery:** The combination of Lactulose and PEG ensures a thorough intestinal cleanse, crucial for medical procedures.
- **Patients with Intolerance to PEG Alone:** Those who experience side effects like nausea, bloating, or discomfort with PEG may find the combination more tolerable.

CONCLUSION

Lactulose remains a widely used and effective agent for the treatment of chronic constipation and bowel preparation due to its safety profile and high efficacy. When combined with PEG, the effectiveness of PEG is significantly enhanced, resulting in better bowel cleansing, reduced side effects, and improved patient adherence. Clinical trials support the use of this combination therapy, especially in populations such as paediatric, pregnant, and geriatric patients. The product Relux L, manufactured by Eskag Pharma Ltd., Kolkata, India, which combines Lactulose and PEG, is particularly beneficial for patients requiring reliable bowel preparation or those intolerant to PEG alone. This combination therapy offers a promising approach for the comprehensive management of constipation across diverse patient groups.

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