Research Article

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Comparative Efficacy and Safety of Polyethylene Glycol vs Lactulose in Chronic Constipation: Non Inferiority Study

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1. Abstract

1.1. Background: Constipation is a common condition. Lactulose & Polyethylene Glycol (PEG) are effective & safe, recommended as first-line medication for Chronic Constipation (CC).

1.2. Aim: To compare the efficacy and safety of PEG 3350 versus lactulose in patients with CC.

1.3. Methods: In this single-center, randomised, open label, parallel-group study. Patients with CC (< 3 bowel movements per 7-day period) received either a 17 g of PEG 3350 or 10 g of lactulose daily for 14 days. Primary endpoint was the number of bowel movements per 7-day period.

1.4. Results: PEG 3350 and lactulose are both effective, increasing the number of bowel movements per week, from 1.6 (95%, CI 1.4, 1.8) in the PEG group and 1.7 (95%, CI 1.5 – 1.9) in the lactulose group at day 0; 3.7 (95% CI 3.3 – 4.3) PEG and 3.8 (95% CI 3.4 – 4.4) Lactulose in first week; 4.2 (95% CI 3.7 – 4.8) PEG and 4.3 (95% CI 3.8 – 4.9) Lactulose in second week, all improvements are statistically significant in the ITT population ($p<0.001$). All constipation symptoms were improved. No significant differences in laboratory finding. Adverse events (AEs) were reported more in PEG 3350 group than lactulose group (17.6% vs 12.7%).

1.5. Conclusions: PEG 3350 and lactulose are both effective for the relief of CC. PEG 3350 was not inferior to lactulose in two cohorts with chronic constipation. Flatulance was less reported in the PEG 3350 group.

2. Introduction

Many studies have attempted to estimate the prevalence of constipation in adult populations and the reported prevalence of constipation varies across studies, ranging from 2% to 30% with the average of 15%. Differences in populations, various factors such as age groups, dietary, culture and environment, may be the reasons for that wide range in prevalence studies. One other important factor may be due

to differences in the way constipation was defined in each study. According to the Rome IV criteria, constipation is used to describe symptoms that relate to difficulties in defecation. These include fewer than 3 spontaneous bowel movements, hard or lumpy stools, excessive straining, sensation of incomplete evacuation or blockage, and the use of manual maneuvers to facilitate evacuation. Chronic constipation is generally defined by symptoms that persist for at least 3 months [1-4].

Initial management of patients with constipation includes lifestyle modification. An increase in dietary intakes and hydration, also moderate physical activity, is an inexpensive and effective method to increase defecation frequency. Osmotic or/and stimulant laxatives should be used as first treatment for patients with chronic constipation when lifestyle and diet modification failed. Osmotic laxatives, such as Polyethylene Glycol (PEG) and lactulose, create an intra-luminal osmotic gradient that prevent the absorption of administered water and increases water into intestinal lumen, resulting in reduced fecal viscosity and increased fecal biomass. Stimulating laxatives, such as bisacodyl and sodium picosulfate, are reducing the absorption of water, and also stimulating intestinal motility by increasing prostaglandin release [5-7]. PEG is also known for its advantages such as high structure flexibility, soluble in water, low intrinsic toxicity that ideally suited for biological application and many more [4, 8-10].

There is good evidence of efficacy and safety, also for long-term treatment, for using PEG with substantial osmotic activity, while lactulose is less effective with more side effects. PEG is an odorless, tasteless, non-absorbable polymer in powder form soluble in water that is not fermented by bacterial flora so that PEG have fewer side effects, such as bloating and flatulence, than lactulose. PEG are high molecular weight, water-soluble polymers that can form hydrogen bonds, resulting in stool softens and more frequent bowel movements [11-13].

3. Methods

3.1. Study Design

This single-center, randomized, open label, parallel-group study; Protocol ID 19-04-0392, Clinicaltrials.gov registration: NCT03957668; was performed between December 2019 and September 2020, compared PEG 3350 and lactulose.

During the first visit (screening), candidates were signing the informed consent. Then, the study candidates be evaluated for enrollment: demographics, medical history, physical examination. Patient diary was given to record how many times defecation during these the following 7 days. Candidates with one or two bowel movement (defecation) during these 7 days continued into the treatment phase. The investigator then allocated eligible patients to a randomization number. Randomization was performed centrally using random permutation blocks of size 4. Patients were randomized into 2 groups depending on the treatment: PEG 3350 (Meiji, Indonesia) or lactulose (Lactulax; Ikapharmindo Putramas, Indonesia).

At the second visit (baseline), hematology, liver and kidney function, electrolytes, urinalysis and fecal occult blood test were examined. Each patient received 10 sachets of PEG 3350 or 1 bottle of 120 ml lactulose syrup, and a new patient diary sheet. During these 7 days, stool frequency, stool consistency was compared with pictures provided, stool passage, and the following symptoms: cramping, rectal irritation, and flatus associated with each bowel movement, recorded in the patient diary sheet.

After 1 week, patient returned the unused drug and the diary sheet. The investigator examined the dairy sheet to look for any improvement of the constipation, then patient received new 10 sachets of PEG 3350 or 1 bottle of 120 ml Lactulose syrup and a new sheet for another week.

After 2 treatment weeks, patients returned the unused drug and the dairy sheet to the investigator. Hematology, liver and kidney function, electrolytes, and urinalysis were examined again to be compared with the previous laboratory results and look for any adverse events.

The patients were called by phone by the co-investigator on day 21 (no drug administered during this last week). The intention was to have information whether any adverse event occurs during this week (by anamnesis).

3.2. Patients

Chronic constipation was defined according to the ROME IV criteria, characterized by 2 or more: straining during >25% of defecations, lumpy or hard stools (Bristol stool form scale 1 or 2) >25% of defecations, sensation of incomplete evacuation >25% of defecations, sensation of anorectal obstruction/blockage >25% of defecations, manual maneuvers to facilitate >25% of defecations, <3 spontaneous bowel movements per week.

Patients were males and females aged ≥ 18 years old, BMI ≥ 18.5, have < 3 bowel movements (defecations) during a 7-day screening period, in otherwise good health as judged by a physical examination and laboratory testing, and not taking medications known to affect bowel function in 1 week before study.

Patients were excluded if they were hypersensitive to the study medication, pregnant, or had a history or evidence of obstructive ileus or Inflammatory Bowel Disease (IBD). Organic bowel disease was ruled out by Fecal Occult Blood Test (FOBT) and/or colonoscopy.

3.3. Study Drugs

Test drug was PEG 3350, given as a powder (17 g) in a sachet, each sachet was dissolved in 220 mL of water, was drunk once daily at bedtime. Comparator drug was lactulose syrup (containing 10 g of lactulose), 15 mL of lactulose was dissolved in 220 mL of water, was drunk once daily at bedtime. PEG 3350 and Lactulose syrup were supplied by PT. Meiji Indonesia.

PEG sachet and Lactulose syrup were packaged by Clinical Research Supporting Unit Faculty of Medicine University of Indonesia for individual patient according to a pre-determined randomization list.

Each drug package was labelled with the patient randomization number and dosage instruction. Each patient was received 10 sachets of PEG 3350 or 1 bottle (120 mL) of lactulose syrup for consumption at day 0 and day 7 (for 7 days each plus a few days in excess). The excess drugs were used for compliance check and to allow additional days for patient visit.

3.4. Study Assessments and Endpoints

Endpoints measured by blinded evaluator. The primary endpoint for efficacy was number of bowel movements (defecation) per 7-day period. The secondary end point were symptom scores: Stool consistency (based on Bristol Stool Form Scale by visual comparison), stool passage (by anamnesis), rectal irritation associated with each bowel movement (by anamnesis), and flatus (by anamnesis). The endpoints for safety were the presence of Adverse Events (AEs), and Serious Adverse Events (SAEs).

3.5. Statistical Analysis

All efficacy analyses were performed on the ITT and PP populations. The ITT population consisted of all randomized patients without eligibility violation who take at least one dose of the study drug and return at least once post-randomization, with Last Observation Carried Forward (LOCF). The PP population included only patients who comply with the study protocol: have consumed at least 75% of total drugs (11 doses from a total of 14 doses).

Statistical analysis of bowel movements frequency was conducted using Generalized Linear Mixed Effect Model (GLMM) with Poisson family and log link function. Non-inferiority was tested using a non-inferiority margin of 1% [per-protocol (PP) population]. Non-inferiority could be concluded if the observed lower limit of the one-sided 95% Confidence Interval (CI) for the difference in response rates (PEG 3350 minus Lactulose) laid completely above the non-inferiority margin. Symptom scores was analysed using friedman's method, and overall rating of effectiveness using Pearson's Chi-squared test. Statistical analyses were performed using SPSS version 25 and R statistics 4.0.3.

After double-blind cross-over design: all patients who take at least one dose of the study drug and return at least once post-randomization, were be subject to safety analysis. All Adverse Events (AEs) and Serious Adverse Events (SAEs) were listed per group (PEG 3350 and lactulose) in the percentage.

4. Results

4.1. Patients Disposition and Baseline Characteristics

This study ran between December 2019 and September 2020, with 190 patients screened and 175 with confirmed chronic constipation (<3 bowel movements in the last week of screening), randomised to receive PEG 3350 (n = 89) or Lactulose (n = 86). Overall, 23 patients withdrew, 13 patients in the PEG group and 10 patients in the Lactulose group. Patient populations are provided in Figure 1. The ITT population comprised 165 patients (PEG, n = 85; Lactulose, n = 80), and the PP population, 152 patients (PEG, n = 76; Lactulose, n = 76). There were no significant differences between groups in the baseline characteristics (Table 1).

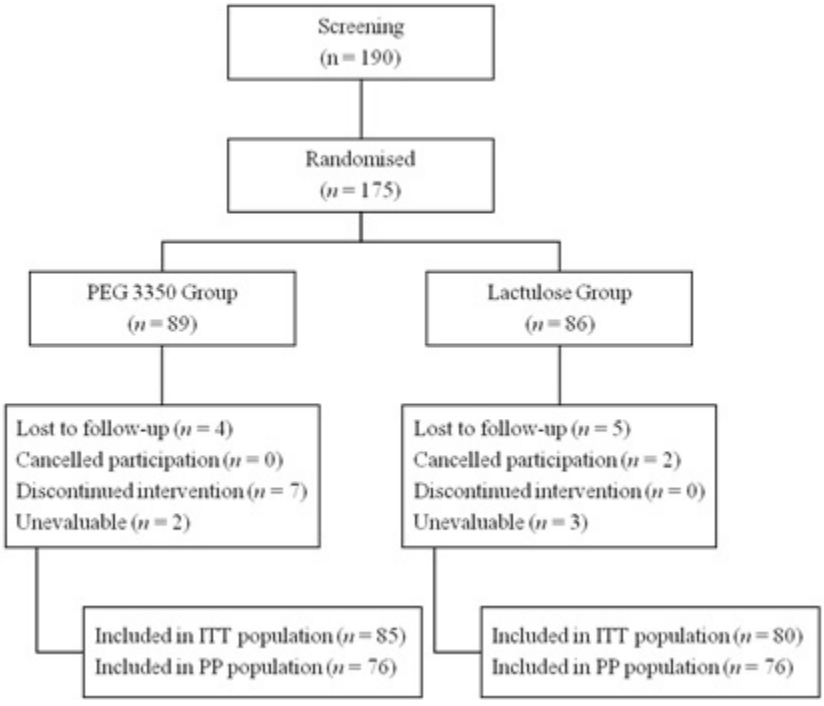

Figure 1: Patient Flow Diagram
ITT: intention to treat; PP: per protocol.

Table 1: Patients' baseline characteristics (ITT population).

No.	Variable	PEG 3350		Lactulose	
		n	%	n	%
1	**Gender**				
	Male	13	15.3	13	16.3
	Female	72	84.7	67	83.8
2	**Age**				
	<40	45	52.9	36	45
	41-60	36	42.4	42	52.5
	>61	4	4.7	2	2.5
3	**BMI**				
	Normal	64	75.3	47	58.8
	Overweight	15	17.6	25	31.3
	Obese	6	7.1	8	10
4	**Comorbidities**				
	Hypertension	8	9.4	7	8.8
	Diabetes Mellitus	3	3.5	4	5
	Renal dysfunction	1	1.2	0	0
	Dyspepsia	10	11.8	4	5.1

BMI: body mass index

4.2. Primary Endpoint

The GLMM model considered two fixed effects, medication and the time of measurement (T0, T1 and T2). Using the null intercept as the reference, this model resulted in an R2 of 0.4, 0.33 and 0.07 using the ITT population for total, fixed effects and random effect, respectively. With similar performance, modeling the PP data resulted in an R2 of 0.4, 0.35 and 0.07 for total, fixed effects and random effect, respectively. Both in PP and ITT population, all medications resulted in a favorable improvement within the first ($p<0.001$) and second week ($p<0.001$). Mean bowel movements frequencies represented as Incidence Rate Ratio (IRR) for each group are provided in Table 2 for ITT population and Table 3 for PP population. Both models demonstrated similar improvement in Lactulose and PEG group, as shown by IRR and 95% CI > 1.

PEG 3350 and lactulose are both effective, increasing the number of bowel movements per week, from 1.6 (95%, CI 1.4, 1.8) in the PEG group and 1.7 (95%, CI 1.5 – 1.9) in the lactulose group at day 0; 3.7 (95% CI 3.3 – 4.3) PEG and 3.8 (95% CI 3.4 – 4.4) Lactulose in first week; 4.2 (95% CI 3.7 – 4.8) PEG and 4.3 (95% CI 3.8 – 4.9) Lactulose in second week, all improvements are statistically significant in the ITT population ($p<0.001$).

PEG group reported a slightly less spontaneous bowel movement but considering the Δ of 10% and a margin of 1, the difference directly imply non inferiority. Within the first week after treatment, both groups resulted in spontaneous bowel movement > 3, which indicates no constipation. The incremental rate of change from week 0 to week 2 is non-linear, as shown in the figure 2. These findings suggested a favorable effect within the first week of treatment, which gradually reduced overtime.

Table 2: Number of Bowel Movements per 7-days period (ITT population)

						95% CI	
	B	**SE**	**z**	***p-value***	**IRR**	**2.50%**	**97.50%**
Lactulose	0.53	0.07	7.8	<0.001	1.7	1.5	1.9
PEG	0.44	0.07	6.4	<0.001	1.6	1.4	1.8
T_1	0.76	0.07	10.3	<0.001	2.1	1.9	2.5
T_2	0.96	0.07	13.6	<0.001	2.6	2.3	3

Table 3: Number of Bowel Movements per 7-days period (PP population)

						95% CI	
	B	**SE**	**z**	***p-value***	**IRR**	**2.50%**	**97.50%**
Lactulose	0.51	0.07	7.3	<0.001	1.7	1.4	1.9
PEG	0.48	0.07	6.7	<0.001	1.6	1.4	1.9
T_1	0.77	0.08	10.2	<0.001	2.2	1.9	2.5
T_2	0.99	0.07	13.5	<0.001	2.7	2.3	3

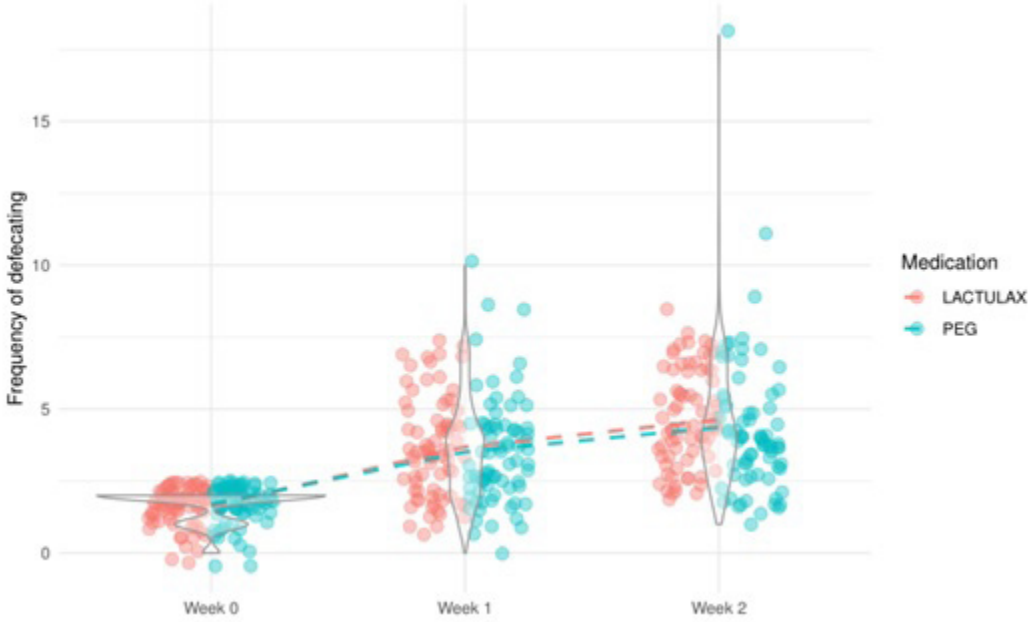

Figure 2: Defecation IRR between two medication groups and different time.

4.3. Secondary Endpoints

Strain stool passage, cramping and rectal irritation proportion were lower in Lactulax group at day 14. In ITT population hard stool consistency proportion was also lower in Lactulax group, but not in the PP population. Patients in the PEG 3350 group had less frequent flatulence than patients in the Lactulax group at day 14. Symptom scores are provided in Table 4 for both ITT and PP population.

All constipation symptoms were improved, but not statistically significant ($p > 0.05$). The proportion of hard stools decreased from 43.64% in the PEG group and 39.39% in the lactulose group at day 0, to 5,45% and 3.03% consecutively at day 14s. Straining decreased from 51.51% to 10.9% in the PEG 3350 groups, and from 47.88% to 5.45% in the lactulose group. Subjects with no cramping and rectal irritation increased from 16.96% to 44.24% in the PEG 3350 group, and from 11.51% to 42.42% in the lactulose group. Subjects with frequent flatus increase from 0.6% to 9.7% in PEG group and 0% to 12.12% in the lactulose group.

4.4. Safety

Twenty-one patients (26.25%) in the lactulose group and 29 patients (34.12%) in the PEG 3350 group reported 1 or more Adverse Events (AEs). The most frequently reported AEs were nausea, bloating, and epigastric pain. Other AEs include abdominal pain, diarrhea, and cephalgia. No Serious Adverse Events (SAEs) were reported Figure 3, Table 5 and 6.

Adverse Events (AEs) were reported more in PEG 3350 group than lactulose group (17.6% vs 12.7%) but not statistically significant. The most common AEs in ITT population were nausea (18.8% vs 13.8%), bloating (9.4% vs 8.8%), epigastric pain (5.9% vs 5%). Other adverse events include abdominal pain (1.2% vs 2.5%), diarrhea (2.4% vs 1.2%), cephalgia (2.4% vs 1.2%), and vomiting 1.2% only in the PEG 3350 group.

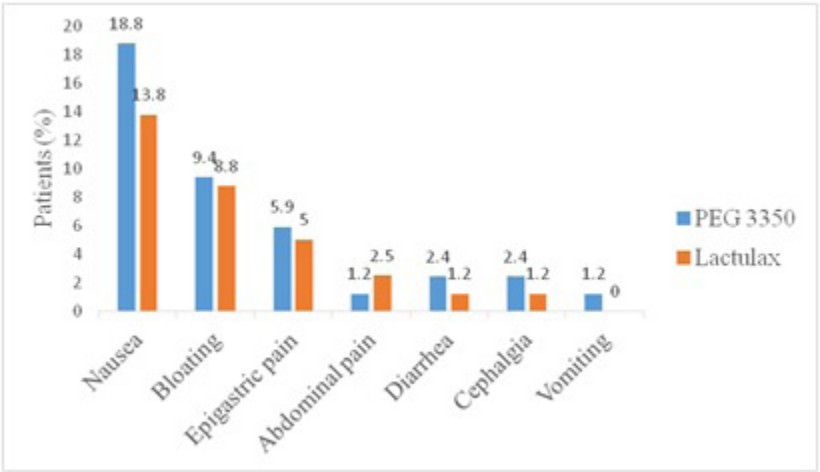

Figure 3: Adverse events (AEs) in both groups

Table 4: Symptom scores

Symptom	ITT Population									PP Population								
	Week 0			Week 1			Week 2			Week 0			Week 1			Week 2		
	Lactulose	PEG	*p*	Lactulose	PEG	*p*	Lactulose	PEG	*P*	Lactulose	PEG	*p*	Lactulose	PEG	*p*	Lactulose	PEG	*p*
Stool Consistency																		
Hard	39.39	43.64		4.48	9.7		3.03	5.45		40.78	42.76		5.26	7.23		3.29	3.29	
Firm	8.48	7.27		13.94	12.12		6.06	6.67		8.55	6.57		13.81	13.15		5.26	7.23	
Soft	0.6	0.6	1	24.85	18.79	0.65	25.45	24.24	0.32	0.65	0.65	1	25.65	19.73	1	26.32	24.34	1
Loose	0	0		4.85	9.7		9.7	10.9		0	0		5.26	9.86		10.53	11.18	
Watery	0	0		0	1.2		4.24	4.24		0	0		0	0		4.6	3.95	
Stool Passage																		
Strain	47.88	51.51		11.51	17.58		5.45	10.9		49.34	50		12.5	15.78		5.92	9.21	
Easy	0.6	0	1	36.36	32.73	0.56	40.61	36.36	0.56	0.65	0	1	36.84	34.21	0.53	41.44	37.5	0.56
Loss of Control	0	0		0.6	1.21		2.42	4.24		0	0		0.65	0		2.63	3.29	
Cramping & Rectal Irritation																		
None	11.51	16.96		33.33	35.15		42.42	44.24		11.84	16.44		34.21	34.21		44.07	43.42	
Mild	30.3	30.9		13.33	15.15		4.85	6.67		30.92	29.6		13.81	14.47		4.6	5.92	
Moderate	6.67	3.03	0.31	1.82	1.21	0.56	1.21	0.61	0.56	7.23	3.28	1	1.97	1.31	1	1.32	0.66	0.56
Severe	0	0.6		0	0		0	0		0	0.65		0	0		0	0	
Have to Continue	0	0		0	0		0	0		0	0		0	0		0	0	
Flatus																		
None	11.51	16.97		5.45	10.91		3.63	5.45		13.15	16.44		5.26	11.18		3.29	5.26	
Moderate	30.3	30.9		23.03	22.42		10.91	15.15		36.18	32.89		24.34	22.36		11.18	14.47	
Occasional	6.67	3.03	0.31	16.36	15.76	0.32	20.61	21.21	0.65	0.65	0.65	1	16.44	14.47	0.17	21.06	20.39	0.65
Frequent	0	0.6		2.42	2.42		12.12	9.7		0	0		2.63	1.97		13.16	9.87	
Very Frequent	0	0		1.21	0		1.21	0		0	0		1.31	0		1.32	0	

Table 5: Adverse events (AEs) in both groups.

Adverse Events	PEG 3350 (n = 85)	Lactulax (n = 80)
Nausea	16	11
Bloating	8	7
Epigastric pain	5	4
Abdominal pain/cramping	1	2
Diarrhea	2	1
Cephalgia	2	1
Vomiting	1	0

Table 6: Adverse Events in ITT and PP Population

	ITT		*p*	PP		*p*
	Non-AEs	AEs		Non-AEs	AEs	
PEG	33.9	17.6	0,31	32.2	17.8	0,38
Lactulax	35.8	12.7		36.2	13.8	

5. Discussion

This study compared PEG 3350 with lactulose in patients with history of constipation based on ROME criteria. To be eligible for enrollment, a patient had to have fewer than three satisfactory bowel movements. A total of 175 patients were enrolled with either 17 g/day PEG or lactulose. PEG 3350 and lactulose are both effective, increasing the number of bowel movements per week, from 1.6 (95%, CI 1.4, 1.8) in the PEG group and 1.7 (95%, CI 1.5 – 1.9) in the lactulose group at day 0; 3.7 (95% CI 3.3 – 4.3) PEG and 3.8 (95% CI 3.4 – 4.4) Lactulose in first week; 4.2 (95% CI 3.7 – 4.8) PEG and 4.3 (95% CI 3.8 – 4.9) Lactulose in second week, all improvements are statistically significant in the ITT population ($p<0.001$).

The first choice maintenance therapy for functional constipation is osmotic laxatives. Based on its effectiveness and safety, PEG is the osmotic agent of choice for both children and adults [14]. In terms of increasing stool frequency, recent meta-analyses in the treatment of functional constipation in adults reported that PEG is more effective than lactulose [15].

Multi studies have reported the favor of PEG as treatment of chronic constipation compared other medication [16-20]. Balsey et al in their Systematic review and meta-analysis compares the efficacy of PEG laxatives with placebo or other laxatives. It demonstrates that PEG is a more effective laxative than lactulose in adults with constipation [21]. Polyethylene glycol, an osmotic laxative, increases the mean number of stools per week more effectively than placebo or lactulose in adults with CIC, based on direct meta-analyses [19]. Dipalma et al in their randomized multicenter placebo controlled trial of polyethylene glycol with total of 304 patients were enrolled and received 6-months treatment period in patients with chronic constipation reported that 61% of PEG treatment weeks versus 22% of the placebo weeks were successful ($P < 0.001$) [20]. Another Network meta-analysis recommended PEG with high certainty to improve Bristol score compared with another intervention [22]. PEG was also shown to be safe and effective in geriatric population. Furthermore, it has been shown that PEG is as safe in geriatrics as in general population [23] Ramkumar et al also published a review on the effectiveness of laxatives in adults with chronic constipation. It showed that the use of polyethylene glycol was supported by good evidence (Grade A) [24]. Another review of treatments of constipation in older adults also revealed that osmotic laxatives, such as polyethylene glycol and lactulose, increased stool frequency [25].

In this study, the flatulence of PEG 3350 group was less reported. Flatulence less reported since PEG is not fermented by gut flora and

does not contribute to gas production [7]. There were no significant laboratory findings in this study and adverse events experienced by both of group. Gastrointestinal symptom such as nausea, bloating, vomiting more frequent in PEG group. Dipalma et al in their randomized multicenter placebo-controlled trial of Polyethylene Glycol Laxative for Chronic Treatment of Chronic Constipation with total of 304 patients also reported there were no significant differences in laboratory findings or adverse events except for the gastrointestinal category where diarrhea, flatulence, and nausea were the most frequent with PEG although they were not individually statistically significant compared with placebo [20]. Piche et al also reported the safety of lactulose vs polyethylene glycol in functional constipation and reported that the most frequent AEs with lactulose plus paraffin and PEG were diarrhoea, abdominal distension, nausea and abdominal pain [26].

Potential limitations of this study were the absence of a double-blinding procedure, and the absence of diet and lifestyle control.

6. Conclusion

This study confirmed the efficacy of both PEG 3350 and lactulose for the relief of chronic constipation. PEG 3350 was not inferior to lactulose in two cohorts with chronic constipation. All constipation symptoms were improved. The proportion of stool consistency, stool passage, cramping and rectal irritation improvement was higher in the lactulose group. Flatulence was less reported in the PEG 3350 group.

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