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Comparison of Effectiveness, Tolerability, and Compliance of Pharmacotherapies in Patients with Functional Constipation: A Real-World Evidence Study

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Abstract

Background: Duphalac® bulk, a combination of bulking agents and an osmotic laxative might prove beneficial in the management of functional constipation (FC) as compared to the existing therapies.

Aim: To evaluate and compare the effectiveness, safety, and compliance of Duphalac® bulk with other available therapeutic options for the management of constipation.

Methods: In this retrospective study, electronic medical records (EMRs) of adult patients suffering from FC who were prescribed various dietary fibers or their combinations between May 2021 to September 2021 and visiting healthcare setups/clinics were reviewed. The patients were divided into four groups (2:1:1:1): Group I-Duphalac® bulk; Group II-isabgol alone; Group III-lactitol and isabgol combination; and Group IV-Polyethylene glycol (PEG) and isabgol combination. Effectiveness was determined using the constipation scoring system (CSS). Adverse events and compliance were assessed. Additionally, lipid and glycemic parameters were analyzed.

Results: Out of 110 patients screened, 96 met the inclusion criteria and participated in the study. Majority of the patients (42.7%) received Duphalac® bulk, followed by lactitol and isabgol combination (19.7%), PEG and isabgol combination (18.7%), and isabgol (18.7%). A significant reduction in overall mean CSS was observed among all the groups; however, the maximum decrease (3.49, $p<0.001$) was found in Group I as compared to Groups II (3.28, $p<0.001$), III (2.58, $p=0.001$), and IV (2.50, $p=0.002$). All treatments were well tolerated. Improvements in glycemic and lipid parameters were observed in all groups.

Conclusion: Duphalac® bulk was well tolerated with significant symptomatic improvement in patients suffering from FC.

Introduction

Constipation is defined as a functional bowel disorder that is characterized by persistently arduous, intermittent, or incomplete defecation, which does not meet irritable bowel syndrome (IBS) criteria [1]. It is a common disorder that can develop from several causes. After precluding the secondary causes of constipation, chronic idiopathic or primary constipation can be categorized as functional defecation disorder, slow-transit constipation, and constipation-predominant irritable bowel syndrome [2]. According to the Rome IV diagnostic criteria for FC, the symptoms include two or more of the following: straining in more than 25% of defecations, lumpy or hard stools in more than 25% of defecations, a sensation of incomplete evacuation in more than one-fourth (25%) of defecations, a sensation of anorectal obstruction/blockage in more than one-fourth (25%) of defecations, manual maneuvers to facilitate in more than one-fourth (25%) of defecations, and fewer than three spontaneous bowel movements per week [3].

Constipation is usually considered a mild condition, but it can lead to serious complications and impaired health-related quality of life, which in turn adds to the economic burden if left untreated [4]. Lifestyle and dietary modifications are considered the first steps in the treatment of chronic constipation [5]. A few dietary intervention studies have observed the effects of fiber intakes, from various dietary sources, on chronic constipation and demonstrated their favorable effects on constipation, with overall reduction rates ranging between 13% [6] and 27% [7] or 0.4% [8] and 4.0% [9] per 1g intake per day.

Wheat dextrin is a soluble, non-viscous dietary fiber consisting of non-digestible glucoside linkages that lead to incomplete hydrolyzation so that only a small percentage of wheat dextrin is absorbed in the small intestine, and the rest is slowly fermented in the large intestine. Soluble fibers ferment to short-chain fatty acids (SCFAs) that improve laxation and regularity by increasing the bulk and weight of stool, and by increasing the water-holding capacity of feces [10]. Fructooligosaccharides (FOS) are indigestible and non-absorbable oligosaccharides fermented in the colon by the resident microflora. During the process of fermentation, FOS is also metabolized to SCFAs [11, 12]. Polydextrose is another soluble dietary fiber reported to increase the fecal bulk and soften stools. Moreover, it also stimulates intestinal peristalsis and increases the defecation frequency [13]. Laxatives (such as PEG and lactulose), which work by persuading bowel movements and facilitating defecation through distinct mechanisms of action, are reserved for patients who do not respond to non-pharmacological approaches [14]. Lactulose, a synthetic disaccharide, is an osmotic laxative that helps in managing FC by increasing stool frequency [15].

Though several clinical trials have been conducted to assess the efficacy and safety of wheat dextrin, FOS, polydextrose, and lactulose individually, there exists a lacuna in the real world for assessing the effectiveness and tolerability of their combination. Other therapeutic options like lactitol [16], PEG [17] (an osmotic laxative), and isabgol [18] (bulking agent) are also used to manage FC, yet real-world comparative studies are scarce. Hence, this pilot study was conceptualized to evaluate the effectiveness, tolerability, and compliance to the combination of wheat dextrin, FOS, polydextrose, and lactulose (Duphalac® bulk) in comparison with other available treatment options (isabgol alone, lactitol, and isabgol combination, PEG and isabgol combination) for FC to generate real-world evidence.

Methods

This was an EMR-based retrospective, observational, multicentre study designed to collect the data from outpatient settings of multiple healthcare setups/clinics (n = 4) across various regions of India.

Study Population

Patients >18 years of age who were diagnosed with FC as per ROME IV criteria were included in the study. The patients with IBS with constipation, opioid-induced constipation, and functional defecation disorders were excluded from the study. Further, patients who underwent gastrointestinal surgery or abdominal surgery within one year prior to the start of screening assessment; patients with a history of gastrointestinal resection; and patients with severe renal or hepatic disorders were excluded.

After reviewing patients' EMR data, patients were divided into four groups (in 2:1:1:1 ratio): Group I, who had received Duphalac® bulk; Group II, who had received isabgol alone; Group III, who had received lactitol and isabgol combination; and Group IV who had received PEG and isabgol combination. The patients of different groups took the respective treatment as oral dosage according to the prescribed information, package insert, or physician's discretion for a minimum period of 21 days, and patients were assessed at/after 28 days

Outcomes

Patients' data were assessed for their demographic characteristics, comorbidities, concomitant medications, and clinical characteristics. The effectiveness of treatment was determined by using a validated constipation scoring system (CSS). In CSS, 8 parameters are monitored, and the total score is obtained by adding the scores of these 8 individual parameters, and the change in CSS score is compared before and after the treatment. However, in the present study, the data of only 5 parameters could be collected from the EMR database, that may be because these are the most frequent parameters capturesd in the routine clinic and hospital settings. Therefore, the efficacy of the Duphalac® bulk was assessed by mean reduction in these 5 scores captured after 1 month and compared with the other groups. The tolerability of the Duphalac® bulk was assessed and compared with other therapies in terms of incidence of adverse events (AEs) during the treatment period (1 month). Further, compliance to therapy was assessed by confirming if ≥80% of prescribed doses were taken, based on the prescription-refill records, reported by the physicians. Additionally, the percentage of patients with improved lipid and glycemic parameters in all four groups was analyzed.

Statistical Analysis

Data analysis was done using R studio 3.5.3. Descriptive statistics were presented in the form of categorical and continuous variables. Categorical variables (like gender) were expressed as percentages and compared using the Chi-square/Fisher exact test, while continuous variables (like age and scores) were expressed as means and compared using T-test and ANOVA. Statistical significance was considered with $p<0.05$. Propensity score matching was used to reduce the selection bias in the study.

Ethical Statement

This was a retrospective study, and the existing medical records that were available as of the date of the Ethics Committee (EC) submission were used for the study without any additional prospective components for research purposes. The patient's confidentiality was maintained using anonymized and de-identified data at the source level. Hence, the process did not necessitate the obligation to obtain informed consent [19]. Accordingly, permission for an Informed Consent Form (ICF) waiver was obtained from an Independent Ethics Committee before the initiation of the data collection process for this study.

Results

Baseline Characteristics

A total of 110 EMRs of FC patients were screened, out of which 96 met the eligibility criteria and were considered for further analysis (Figure 1). Among these, the majority of the patients (42.7%) received Duphalac® bulk, followed by lactitol and isabgol combination (19.7%), PEG and isabgol combination (18.7%), and isabgol (18.7%). The mean age of the patients was 47.4 ± 14.7, 41.2 ± 11.8, 38.8 ± 12.1, and 48.0 ± 10.6 years in Groups I, II, III, and IV, respectively. An equal number of males (48) and females (48) were presented with FC. The patients were from multiple centers located across the country, with the maximum number of patients from Rajasthan (35.4%). Overall, the baseline characteristics were comparable among the groups (Table 1).

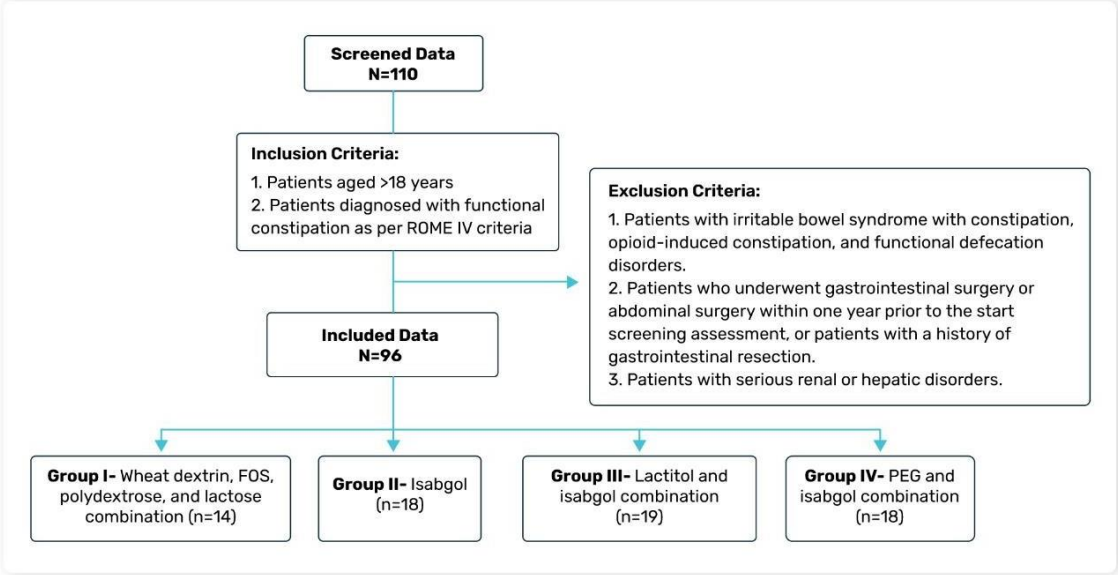

Figure 1: Data inclusion flow chart

Majority of the patients had cardiovascular (32.2%) and endocrinological comorbidities (27.0%) with hypertension (18.7%) and diabetes mellitus (21.8%) being the major comorbidities within the groups, respectively. Most of the patients were taking gastrointestinal medications (48.9%), followed by nutritional supplements (25.0%), cardiovascular (15.6%), and others (41.6%).

The chief complaints reported by the patients of FC included difficulty in defecation (62.5%), straining while passing stools (36.5%), feeling of incomplete evacuation (29.2%), passage of hard stools (26.0%), anorectal blockage (15.6%), and manual maneuver (13.5%). Some patients also complained about symptoms other than FC, including stomach-ache (26.0%) and minor complaints like body-ache, dizziness, allergic rhinitis, etc.

Table 1: Baseline Characteristics of the Patients

Parameters	Total	Group I	Group II	Group III	Group IV
	N = 96	n = 41	n = 18	n = 19	n = 18
Age (Years)					
Mean ± SD	NA	47.4 ± 14.7	41.2 ± 11.8	38.8 ± 12.1	48.0 ± 10.6
Range	NA	(18-76)	(21-60)	(23-61)	(33-72)
Gender (n, %)					
Male	48 (50.0%)	20 (48.8%)	12 (66.7%)	6 (31.6%)	10 (55.6%)
Female	48 (50.0%)	21 (51.2%)	6 (33.3%)	13 (68.4%)	8 (44.4%)
Height (cm)	NA	163.0 ± 7.5	163.1 ± 10.3	159.5 ± 8.0	160.9 ± 9.8
Weight (kgs)	NA	64.9 ± 9.4	68.0 ± 9.8	60.1 ± 7.6	65.0 ± 10.2
Heart Rate	NA	18.2 ± 3.1	16.9 ± 3.1	17.1 ± 3.0	17.9 ± 3.0
Blood Pressure					
SBP	NA	124.9 ± 11.5	129 ± 10.2	119.0 ± 8.4	130.2 ± 9.8
DBP	NA	80.9 ± 7.6	81.3 ± 5.9	78.1 ± 6.5	82.3 ± 4.5
Residence					
Rajasthan	34 (35.4%)	14 (34.1%)	6 (33.3%)	7 (36.8%)	7 (38.9%)
Uttar Pradesh	23 (23.9%)	8 (19.5%)	7 (38.9%)	5 (26.3%)	3 (16.7%)
Telangana	20 (20.8%)	13 (31.7%)	0 (0%)	2 (10.5%)	5 (27.8%)
West Bengal	15(15.6%)	6 (14.6%)	3 (16.7%)	3 (15.8%)	3 (16.7%)
Delhi	2 (2.0%)	0 (0%)	1 (5.6%)	1 (5.3%)	0 (0%)
Haryana	2 (2.0%)	0 (0%)	1 (5.6%)	1 (5.3%)	0 (0%)
Comorbidities (n)					
Cardiovascular	31 (32.2%)	18 (43.9%)	7 (38.9%)	1 (5.3%)	5 (27.8%)
Hypertension	18(18.7%)	11 (26.8%)	4 (22.2%)	1 (5.3%)	2 (11.1%)
Dyslipidaemia	7 (7.2%)	3 (7.3%)	2 (11.1%)	0 (0%)	2 (11.1%)
Coronary artery disease	6 (6.2%)	4 (9.8%)	1 (5.6%)	0 (0%)	1 (5.6%)
Endocrinological	26 (27.0%)	10 (24.4%)	3 (16.7%)	7 (36.8%)	6 (33.3%)
Diabetes mellitus	21 (21.8%)	7 (17.1%)	3 (16.7%)	5 (26.3%)	6 (33.3%)
Hypothyroidism	5 (5.2%)	3 (7.3%)	0 (0%)	2 (10.5%)	0 (0%)
Others*	19 (19.7%)	8 (19.5%)	3 (16.7%)	3 (15.8%)	5 (27.8%)
*Others include anxiety, uterine fibroid, hyperuricemia, left renal calculus, LRTI, arthropathy, rheumatoid arthritis, GERD, lipoma, non-erosive gastritis, psoriasis, sleep apnoea, and obesity.					
Concomitant Medications (n)					
Gastrointestinal medications	47 (48.9%)	18 (43.9%)	9 (50.0%)	12 (63.1%)	8 (44.4%)
Nutritional Supplements	24 (25.0%)	8 (19.5%)	7 (38.8%)	7 (36.8%)	2 (11.1%)
Cardiovascular medications	15 (15.6%)	10 (24.3%)	4 (22.2%)	1 (5.2%)	-
*Other medications	40 (41.6%)	15 (36.5%)	9 (50.0%)	10 (52.6%)	6 (33.3%)
Clinical Characteristics					
Difficulty in defecation	60 (62.5%)	26 (43.3%)	11 (18.3%)	12 (20.0%)	11 (18.3%)
Straining while passing stools	35(36.5%)	17 (28.3%)	6 (10.0%)	7 (11.7%)	5 (8.3%)
Feeling of incomplete evacuation	28 (29.2%)	12 (20.0%)	5 (8.3%)	5 (8.3%)	6 (10.0%)
Passage of hard stools	25 (26.0%)	14 (23.3%)	4 (6.7%)	3 (5%)	4 (6.7%)
Anorectal blockage	15 (15.6%)	6 (10%)	3 (5%)	2 (3.3%)	4 (6.7%)
Manual maneuver	13 (13.5%)	4 (6.7%)	3 (5.0%)	3 (5.0%)	3 (5.0%)
Stomach-ache	25 (26.0%)	16 (26.7%)	2 (3.3%)	3 (5.0%)	4 (6.7%)
Others (Body-ache, dizziness, allergic rhinitis)	14 (14.6%)	6 (10%)	5 (8.3%)	2 (3.3%)	1 (1.7%)
Dose of drug	NA	23.4 ml 20 ml & 30 ml	15 gm	15 gm	8 (15 gm) & 10 (20 gm)
Frequency					
OD	NA	40	18	19	12
BD	NA	1	-	-	6
Mean duration of drug	NA	23.8 days (21-30) days	21 days	21.9 days (21-30 days)	23.5 days (21-30 days)

Efficacy

A significant decrease in overall mean score was observed among all the groups (Figure 2a); however, the maximum decrease (3.49, $p < 0.001$) was found in Group I when compared with Group II (3.28, $p<0.001$), Group III (2.58, $p = 0.001$) and Group IV (2.50, $p = 0.002$). Further, the mean reduction in the frequency of bowel movement score in Group I was found to be higher (0.12, $p = 0.27$) when compared with Groups II (-0.28, $p = 0.13$) and III (-0.11, $p = 0.48$), except for Group IV, though the mean differences between the groups were similar (0.17, $p = 0.43$) (Figure 2b).

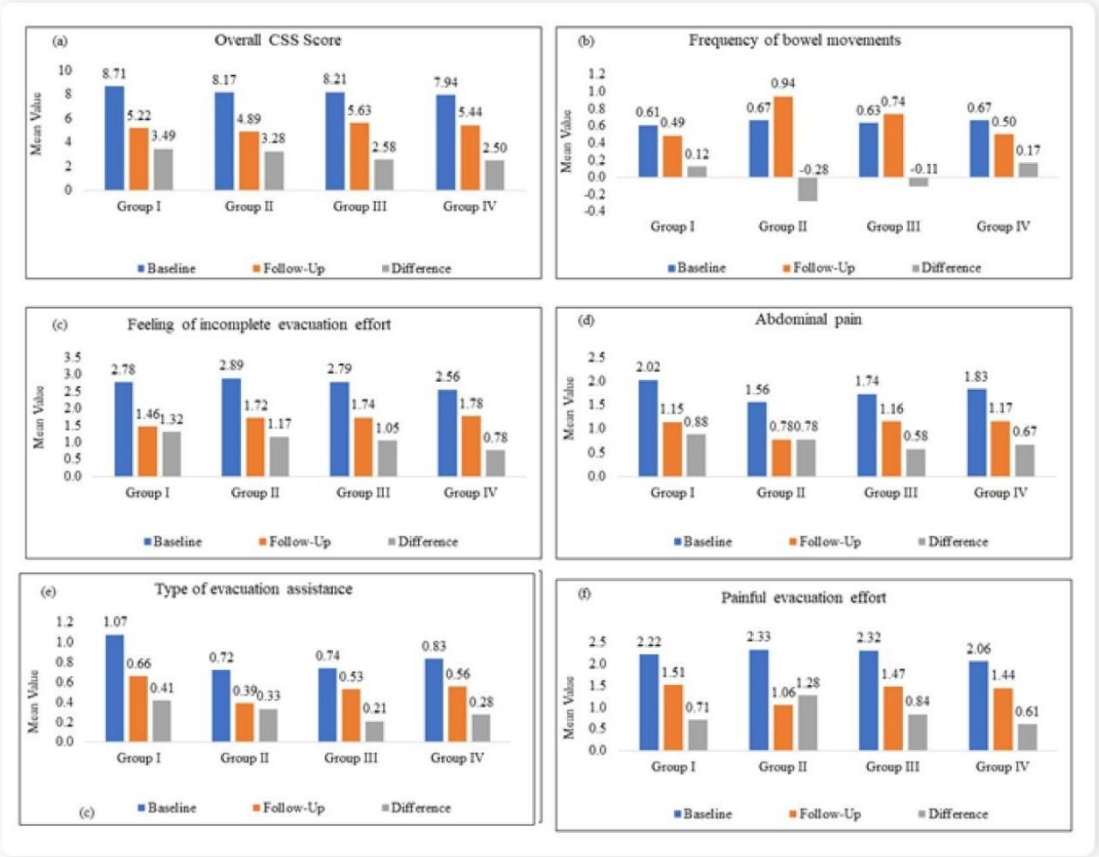

Figure 2: (a) Mean reduction in overall CSS score; (b) frequency of bowel movements; (c) feeling of incomplete evacuation; (d) abdominal pain; (e) type of evacuation assistance; (f) painful evacuation effort

In the case of the incomplete evacuation parameter, the mean score reduction in Group I was significantly higher (1.32, $p < 0.001$) when compared with other groups, with corresponding reductions of 1.17 ($p < 0.001$), 1.05 ($p = 0.00$) and 0.78 ($p = 0.01$) in Groups II, III, and IV, respectively (Figure 2c). The percentage of patients who showed improvements for incomplete evacuation parameters was 73.2%, 83.3%, 68.4%, and 61.1% in Groups I, II, III, and IV, respectively. Similarly, for the parameter of abdominal pain, Group I showed the maximum reduction in symptom score (0.88, $p<0.001$) when compared with other groups, i.e., 0.78 ($p = 0.01$) in Groups II, 0.58 ($p = 0.03$) in III, and 0.67 ($p = 0.02$) in IV (Figure 2d). The percentage of patients who showed amelioration for abdominal pain parameters was 53.7%, 72.2%, 52.6%, and 61.1% in Groups I, II, III, and IV, respectively.

In corollary, the improvement in the type of evacuation assistance parameter was also found to be maximum in Group I (0.41, p<0.001). The mean reduction in symptom scores in Groups II, III, and IV was 0.33 (p =0.03), 0.21 (p = 0.10), and 0.28 (p = 0.03), respectively (Figure 2e). The percentage of patients who exhibited improvement for this parameter was also maximum in Group I (31.7%) when compared with Groups II (27.8%), III (15.8%), and IV (27.8%). For the parameter of painful evacuation effort, Group I performed better than Group IV, with corresponding reductions of 0.71 (p<0.001) and 0.61 (p = 0.03), respectively. However, the mean reduction in symptom score was observed to be higher in Group II (1.28, p<0.001) as well as Group III (0.84, p = 0.00) when compared with Groups I and IV (Figure 2f). The percentage of patients showing improvement for this parameter was 46.3%, 77.8%, 57.9%, and 50% in Groups I, II, III, and IV, respectively.

Tolerability

All treatments were well tolerated with no cases of treatment discontinuation. The percentage of patients who experienced AEs was 4.87% in Group I, 5.5% in Group II, 10.5% in Group III, and 16.6% in Group IV. The most common adverse events reported by the patients included bloating, flatulence, belching, feeling discomfort, cramps, and diarrhea. No serious AEs were reported.

Patient Compliance

The percentage of patients who took ≥80% of prescribed dose regimen of laxatives were found to be maximum in Group I (97.5%) when compared with Groups II (88.88%), III (94.7%), and IV (94.4%).

Glycemic Control

The percentage reduction in mean fasting plasma glucose (FPG) was found to be 4.2%, 8.0%, 2.3%, -0.3% in Groups I, II, III, and IV, respectively. Further, the percentage of patients who had shown improvement in FPG was 87.1% in Group I, 90.0% in Group II, 61.5% in Group III, and 53.3% in Group IV. Similarly, the percentage reduction in mean post-prandial plasma glucose (PPG) was observed to be 3.4%, 7.5%, -1.3%, and 1.7% in Groups I, II, III, and IV, respectively, and the percentage of patients who had improvement in PPG was 74.2% in Group I, 90.0% in Group II, 46.2% in Group III, and 60.0% in Group IV (Figure 3).

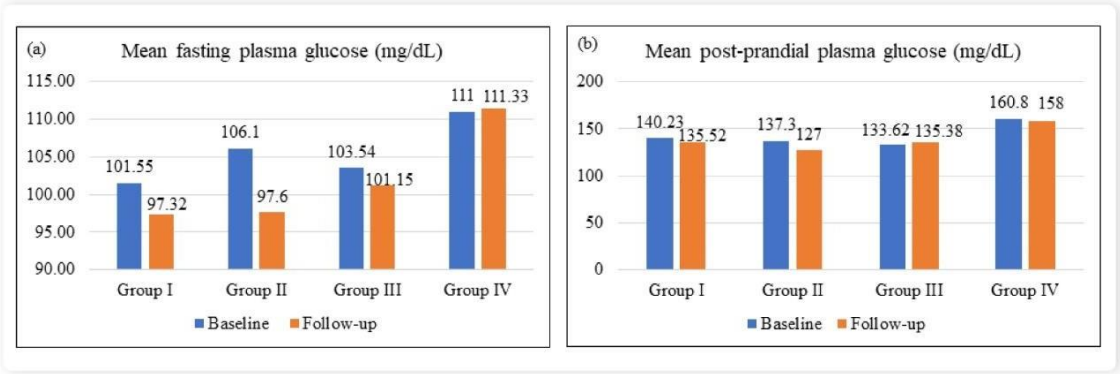

Figure 3: Mean reduction in (a); fasting plasma glucose (b); post-prandial glucose

Lipid Control

The percentage reduction in mean total cholesterol (TC) level was observed to be 4.6% in Group I, 2.8% in Group II, 3.7% in Group III, and 2.8% in Group IV. The percentage of patients who showed improvement was 83.3%, 69.2%, 91.7%, and 85.7% in Groups I, II, III, and IV, respectively. Similarly, decreases were seen in mean low-density lipoprotein (LDL) levels at 2.5%, 4.4%, 3.9%, and 2.4% in Groups I, II, III, and IV, respectively. The corresponding percentage of patients who had shown improvement was 66.7%, 88.9%, 81.8%, and 71.4% in Groups I, II, III, and IV, respectively. The percentage decline in mean very-low-density lipoprotein (VLDL) level was reported to be 4.3%, 10.7%, 4.7%, and 3.4% in Groups I, II, III, and IV, respectively, with the corresponding percentage of patients with improvement was 56.7%, 77.8%, 72.7%, and 64.3%, respectively.

The percentage increase in mean high-density lipoprotein (HDL) level was observed to be 4.8% in Group I, 8.1% in Group II, 6.4% in Group III, and 0.7% in Group IV. The percentage of patients who demonstrated an increase in HDL level was 66.7%, 88.9%, 63.6%, and 42.9%, respectively. Further, the percentage decrease in mean triglyceride (TG) level was reported to be 6.5%, 10.3%, 4.0%, and 4.8% in Groups I, II, III, and IV, respectively, and the corresponding percentage of patients with improvement was 70.0%, 77.8%, 72.7%, and 85.7% (Figure 4).

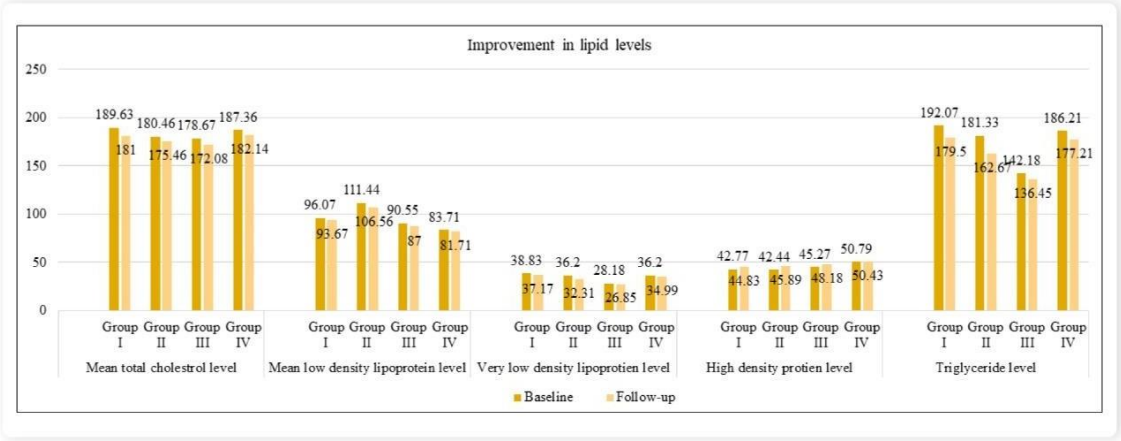

Figure 4: Improvement in lipid levels

Discussion

It is common knowledge that constipation increases with age, and it is evident by the studies that reported about 65% of the patients suffering from constipation are older than 60 years [20,21]. In consonance, in the present study, the upper bound of the age of the patients also crossed 60 years in all the groups. Further, the female population is reported to be at a higher risk for constipation, which could be attributed to slower transit, pelvic floor dysfunction due to obstetric trauma, harder stool forms, and over-reporting [22,23]. However, in the current study, there was an equal distribution of males and females (1:1). Most patients were observed to have comorbidities like diabetes and hypertension. These findings are consistent with other studies reporting a higher prevalence of diabetes (10%) and hypertension (16%) in Indian patients with FC [24].

The symptoms of constipation are difficult to treat, and lack of dietary fiber is believed to be the most common reason behind constipation [25]. Therefore, increasing the dietary fiber intake is recommended as the first line of therapy [26]. with 25 g/day considered effective [27]. The dietary fibers are believed to relieve the symptoms of constipation by the following mechanism of action: a) increases stool bulk and hastens colon transit; b) fermenting fiber generates SCFAs (butyrate, propionate, acetate, etc.), which enhances osmotic load and colon transit; c) SCFAs alter the intraluminal biomass directly or indirectly by reducing luminal pH, which accelerates colon transit; and d) water-retaining capacity of fibers stimulate the gastrointestinal motility by increasing fecal bulk [28]. The combination of bulking agents such as dietary fibers and an osmotic laxative act as hyperosmolar agents, which increases the water content of stool, making it softer and easier to pass. Moreover, they increase the fecal mass, with resultant bowel distension, and promote intraluminal pressure, which ultimately works as a mass reflex in the colon [29].

In the present study, a significant reduction in overall CSS score was observed in Group I, indicating a substantial improvement in symptoms of FC in patients who were prescribed the combination of dietary fibers and a laxative. Further, when compared to other groups, Group I exhibited the maximum reduction in overall CSS, demonstrating it be more effective than other groups (patients who had taken dietary fibers alone), indicating the synergistic effects of the combination of a laxative with dietary fibers. After evaluating the individual parameters, a significantly higher improvement was found in most parameters such as frequency of bowel movements, incomplete evacuation effort, abdominal pain, type of evacuation assistance in Group I as compared to the other groups, except for painful evacuation effort. On similar lines, Cassettari et al. (2019) evaluated the effect of the combinations of dietary fiber (green banana biomass) anddifferent laxatives (PEG 3350 and sodium picosulfate) in the treatment of FC in children and adolescents. The study reported a statistically significant increased proportion of patients with symptomatic relief (>3 bowel movements/week) in patients treated with a combination of dietary fiber and laxatives but not in patients treated with dietary fiber alone [30].

The AEs recorded in the current study were reported by only a few numbers of patients, and these AEs were bloating, flatulence, belching, feeling discomfort, cramps, and diarrhea. This might be due to the fermentation of dietary fibers after ingestion, which leads to the production of gas, resulting in undesirable discomfort, bloating, and flatulence. Generally, AEs are poorly reported by researchers in the case of dietary fibers.31 In consistence with the findings of the present study, the combined symptom score for gastrointestinal side effects (abdominal pain, flatulence, borborygmi, and bloating) was reported to be higher in patients taking rye bread compared with those taking low-fiber rye toast and the control group [7]. The lower incidence of side effects might be the reason for the good compliance shown by the patients in the present study.

Besides improving constipation, glycemic and lipid parameters were also observed in the patients taking dietary fibers. These observations agree with the existing literature stating that dietary fibers exert a hypoglycemic effect by delaying digestion and absorption of carbohydrates after getting converted into viscous gels post-dissolution [32] Dietary fibers also ameliorate lipid levels due to their low energy levels, bulking effect, high viscosity, and binding capacity to cholesterol resulting in lower absorption and greater excretion [33]. Various researchers have reported the hypoglycemic and lipid-lowering effects of wheat dextrin [34], FOS [35], and polydextrose [36] as these are found to significantly decrease FPG, PPG, TC, LDL, TC/HDL, and LDL/HDL ratios, triglyceride, and VLDL-cholesterol; and increase HDL and insulin levels.

The current study is a retrospective pilot study, the sample size was low. Data for all the parameters of CSS were not available, which is one of the limitations of the study.

Conclusion

Dietary fibers provide significant symptomatic relief in patients with FC as determined by CSS. While lactulose, an osmotic laxative, is a holistic treatment for constipation due to its prebiotic effect, its addition of soluble dietary fibers (Duphalac® bulk) showed a synergistic effect by demonstrating the maximum reduction in mean CSS score as compared to the dietary fibers alone. Therefore, the present study's findings emphasize the use of a combination of dietary fibers and laxatives for patients with FC, but larger studies are warranted to confirm these findings.

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Conflict of Interest: Nil

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