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Original Article

Analysis of the efficacy of lactulose combined with polyethylene glycol in the treatment of functional constipation

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Abstract: Objectives: This study focuses on analyzing the efficacy of lactulose oral solution combined with Macrogol 4000 Powder in the treatment of functional constipation (FC). Methods: A total of 125 FC patients were selected, with 60 cases in a control group, who were treated with lactulose oral solution alone, and 65 cases in a research group, who were treated with lactulose oral solution combined with Macrogol 4000 Powder. The two groups were analyzed and compared in terms of efficacy, symptom recovery, Bristol Stool Form Scale (BSFS) and Wexner Constipation Scale (WCS) scores, adverse effects, serum indices, and Patient Assessment of Constipation Quality of Life (PAC-QOL). Univariate and multivariate analyses were performed to identify risk factors affecting the efficacy. Results: The total response rate of treatment in the research group was higher than that in the control group, and the symptom recovery was significantly better in the research group. In addition, the research group showed markedly elevated BSFS scores and reduced WCS scores after treatment as compared to the control group. Furthermore, significantly better improvements in various serum indices were determined in the research group. There was no remarkable difference in the incidence of total adverse reactions between groups. Finally, the course of disease, hypertension, diabetes, hyperlipidemia, and therapeutic method were identified to be factors affecting treatment efficacy in patients with FC. Conclusions: The efficacy therapeutic of lactulose oral solution combined with Macrogol 4000 Powder in the treatment of FC is promising.

Keywords: Lactulose oral solution, Macrogol 4000 powder, functional constipation, efficacy

Introduction

Constipation is an abnormal phenomenon of defecation, which belongs to common functional problems of the digestive system and can be specifically manifested as abnormalities in the frequency of defecation, stool trait, time of defecation, and strength of defecation [1]. Its etiology is related to colonic sensorimotor disorders and pelvic floor dysfunction, which may be secondary to diet, medications, metabolic disorders, endocrine disorders, psychiatric disorders, or gastrointestinal obstruction; and if it is not related to secondary factors such as those mentioned above, then the diagnosis of functional constipation (FC) is confirmed [2, 3]. FC, as a chronic gastrointestinal disorder, poses a greater socioeconomic burden, and its treatment is difficult and challenging [4]. Statistically, FC is common not only in children but also in adults and is more prevalent in women [5, 6]. The risk of constipation in the general population is 16.5%, while the risk of FC can be up to 9.2% [7]. There are currently no reliable pharmacological options for the treatment of FC, and further trials are needed to explore the therapeutic options for this group of patients [8]. This study is a relevant trial from the perspective of drug therapy and hopefully contributes to the treatment of FC.

Lactulose is a disaccharide, consisting of galactose and fructose, which can be utilized as an osmotic laxative for constipation treatment [9]. It can regulate parameters such as fecal frequency, volume and weight in the patient's organism by generating an osmotic gradient and increasing water retention in the feces [10]. Previous studies have confirmed that it can also be used in the treatment of constipation in

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patients with type 2 diabetes and does not significantly affect patients' blood glucose levels [11]. Its oral solution for the treatment of FC patients was found to significantly increase the frequency of bowel movements, with a relatively low overall risk of recurrence [12]. Macrogol 4000 Powder is also an osmotic laxative, essentially a mixture of glycol polymers, which is biologically inert, non-absorbable and well tolerated, and can be applied in the treatment of chronic idiopathic or FC in children and adults [13]. Its mechanism is like that of lactulose in the treatment of constipation, which improves colonic functioning in the patient, frequency of defecation, fecal consistency, as well as increasing the amount of fecal water excreted, without significantly affecting the balance of intestinal microorganisms or causing adverse events such as electrolyte disorders [14, 15]. It has also been used in the treatment of elderly patients with chronic constipation and has been shown to be clinically effective, well tolerated, and is safe and reliable for long-term use [16].

Currently, clinical studies on lactulose oral solution combined with Macrogol 4000 Powder for the treatment of FC are relatively limited, so this study aims to analyze and report in detail from this aspect.

Materials and methods

Patient information

This retrospective study was approved by Suining Central Hospital Ethics Committee. Inclusion criteria: patients were diagnosed with FC [17]; those that had not used laxatives, prokinetic drugs, or other therapies for constipation in the last 2 weeks; the number of bowel movements was less than 3 per week; and the patients had good compliance and agreed to cooperate with the treatment. Exclusion criteria: allergy to the drugs used in this study; secondary constipation caused by other diseases; accompanied by other gastrointestinal disorders; pregnant or breastfeeding women; combination of impaired cardiac, pulmonary, or renal functions; and poor compliance. A total of 125 FC patients admitted to Suining Central Hospital from March 2022 to January 2024 were selected after screening according to the above inclusion and exclusion criteria. Among them, 60 cases in the control group were treated with lactulose oral solution alone; while 65 cases in the research group were treated with lactulose oral solution combined with Macrogol 4000 Powder.

Methods

The control group was treated with lactulose oral solution alone, 5 to 10 mL/dose, 1 time/d. In the research group, the treatment was combined with additional Macrogol 4000 Powder. The powder was taken with warm water after dinner, 10 g each time, once a day. All groups were treated continuously for 14 d.

Outcome measures

(1) Efficacy [18]. Markedly effective: the symptoms of constipation disappeared with defecation once a day, which was formed and soft stools; effective: the symptoms of defecation difficulty improved with defecation once a day, which was formed and cracked; ineffective: the symptoms showed no improvement. (2) Symptom recovery. The degree of defecation, stool trait and time of defecation were recorded in both groups, with each score ranging from 0-3, and the scores were proportional to the severity of symptoms [19]. For degree of defecation, no sense of incomplete defecation was recorded as 0 points, mild sense of incomplete defecation as 1 point, obvious sense of incomplete defecation but not affecting life and work as 2 points, and obvious sense of incomplete defecation affecting life and work as 3 points; for stool trait, normal was recorded as 0 points, dry and cracked as 1 point, clumping as 2 points, separated as hard clumps was 3 points; for time of defecation, 1 time/d was recorded as 0 points, 1 time/2-3 d as 1 point, 1 time/4-5 d as 2 points, 1 time >6 d as 3 points. (3) Bristol Stool Form Scale (BSFS) and Wexner Constipation Scale (WCS) scores [20]. The BSFS scale was used to assess fecal traits on a scale of 1 to 7, with 1 being separate hard lumps and 7 being watery stools. The WCS was used to assess the severity of constipation, with a score ranging from 0 to 30, and the score is proportional to the severity of the condition. (4) Adverse reactions [21]. The number of cases with adverse events such as diarrhea, abdominal distension, abdominal pain, nausea and vomiting after treatment was observed and recorded, and the incidence rate was calculated. (5) Serum indices [22]. About 4 mL of

Table 1. Comparison of general data between both groups

Indexes	Control group (n=60)	Research group (n=65)	χ^2/t	P
Sex			0.013	0.909
Male	28 (46.67)	31 (47.69)		
Female	32 (53.33)	34 (52.31)		
Age (year)	46.75 ± 7.95	47.45 ± 8.40	0.478	0.634
BMI (kg/m^2)	22.17 ± 2.06	22.62 ± 2.77	1.024	0.308
Course of disease (week)	5.07 ± 1.58	5.43 ± 2.24	1.030	0.305
Combined hypertension			0.437	0.509
Yes	6 (10.00)	9 (13.85)		
No	54 (90.00)	56 (86.15)		
Combined diabetes			0.538	0.463
Yes	9 (15.00)	13 (20.00)		
No	51 (85.00)	52 (80.00)		
Combined hyperlipidemia			0.426	0.514
Yes	11 (18.33)	15 (23.08)		
No	49 (81.67)	50 (76.92)		

Note: BMI, body mass index.

patients' early morning fasting venous blood was drawn before and after treatment, and the serum was obtained after centrifugation. The nitric oxide (NO) and substance P (SP) were determined by radioimmunoassay, and the level of growth inhibitory hormone (GHIH) was measured by enzyme-linked immunosorbent assay. (6) Quality of life. Changes in the quality of life of the 2 groups before and after treatment were assessed using the Patient Assessment of Constipation Quality of Life (PAC-QOL score) [23], which included psychological discomfort, physical discomfort, satisfaction, worry, and anxiety. Using a 5-point scale assigning a score of 0-4, this scale indicates worse quality of survival with higher scores.

Statistical processing

Measurement data were expressed as ($\bar{x} \pm s$), and independent samples t-test and paired t-test were used to analyze the intergroup and intragroup differences. Counting data were expressed using rates (percentages) and compared by X^2 test between groups. Binary Logistic multivariate regression analysis was used to explore risk factors affecting patient efficacy. The collected experimental data were analyzed using SPSS 21.0. P<0.05 indicates a statistically significant difference. In addition, the sample size of this study strictly followed the inclusion and exclusion criteria for screening, and met the minimum sample size requirement per group (approximately 58 cases) calculated by the sample size estimation formula (as shown below):

$$n = \left(\frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times p(1-p)}{p_2 - p_1} \right)^2$$

Results

No notable difference in general data between the two groups

Female participants accounted for 53.33% and 52.31%, respectively in the control group and the research group. The ages of the control and research groups were (46.755 ± 7.95) years and (47.45 ± 8.40) years, respectively, while the body mass indices (BMI) were (22.17 ± 2.06) kg/m^2 and (22.62 ± 2.77) kg/m^2, respectively, and the disease courses were (5.07 ± 1.58) weeks and (5.43 ± 2.24) weeks, respectively. The proportions of those with hypertension, diabetes, and hyperlipidemia in the control group were 10.00%, 15.00%, and 18.33% respectively, compared to 13.85%, 20.00%, and 23.08% in the research group. After analysis, general data such as gender, age, BMI, course of disease, and comorbidities of hypertension, diabetes, and hyperlipidemia did not differ significantly between groups (P>0.05) (**Table 1**).

Table 2. Comparison of efficacy between both groups

Indexes	Control group (n=60)	Research group (n=65)	χ^2	P
Markedly effective	24 (40.00)	34 (52.31)		
Effective	19 (31.67)	25 (38.46)		
Ineffective	17 (28.33)	6 (9.23)		
Total efficacy	43 (71.67)	59 (90.77)	7.583	0.006

The research group exhibited better treatment efficacy

The total effective rate of treatment in the control group was 71.67%, and that in the research group was 90.77%. There was a remarkable difference in the total effective rate of treatment between the two groups (P=0.006). See **Table 2**.

Analysis of risk factors affecting efficacy

To further enhance efficacy and deeply explore the potential intervention methods for improving the curative effect on FC, we conducted an in-depth analysis of factors influencing patient efficacy, which can be helpful for further optimizing the clinical management of patients. Of all the patients, ineffective treatment was found in 23 cases and effective treatment in 102 cases. Taking the effectiveness of treatment as the dependent variable and the collected clinical data as independent variables, a univariate analysis was carried out, and it revealed that gender, age, and BMI had no significant relationship with treatment efficacy (P>0.05). Subsequently, factors with significant differences, such as the course of disease, hypertension, diabetes, hyperlipidemia, and therapeutic method, were used as independent variables in a binary Logistic multivariate regression analysis. The course of disease (P=0.004), hypertension (P=0.007), diabetes (P=0.002), hyperlipidemia (P=0.001), and therapeutic method (P=0.040) were all identified to be risk factors affecting the efficacy (P<0.05). See **Tables 3**-**5** for details.

Symptom recovery was more advantageous in the research group

Symptom recovery after receiving different treatment modalities was analyzed by assessing the degree of difficulty in defecation, stool trait, time of defecation and other symptom-related indicators in both groups. The data indicated that the defecation degree scores of the control and research groups prior to treatment were (2.03 ± 0.55) points and (1.92 ± 0.59) points, respectively, and the corresponding scores after treatment were (1.42 ± 0.7) points and (0.82 ± 0.46) points. The stool trait scores of the control and research group were (2.10 ± 0.66) points and (2.15 ± 0.64) points before treatment and (1.63 ± 0.58) points and (1.17 ± 0.57) points after treatment, respectively. The pre- and post-treatment defecation time scores of the control group were (2.10 ± 0.57) points and (1.42 ± 0.50) points, respectively, while those of the research group were (2.09 ± 0.61) points and (1.00 ± 0.31) points, respectively. The results revealed no remarkable difference in the difficulty degree of defecation, stool trait, and time of defecation before treatment (P>0.05); but all the three indexes appeared to be significantly reduced after treatment in both groups (P<0.05), with lower scores found in the research group than those in the control group (P<0.05). See **Figure 1**.

The improvement in BSFS and WCS scores was better in the research group

Before treatment, the BSFS scores of the control and research groups were (2.32 ± 0.98) points and (2.38 ± 0.84) points, respectively, and after treatment, they increased to (3.17 ± 1.25) points and (4.00 ± 1.47) points, respectively. The WCS scores of the control group before and after treatment were (19.90 ± 3.62) points and (8.17 ± 2.05) points, respectively, and those of the research group were (19.23 ± 3.07) points and (5.91 ± 1.64) points, respectively. The results showed no significant intergroup difference in BSFS and WCS scores before treatment (P>0.05). The BSFS scores of both groups increased after treatment (P<0.05), with higher scores in the research group than in the control group (P<0.05). After treatment, the WCS scores were significantly decreased in both groups (P<0.05), with more

Table 3. Univariate analysis of factors affecting efficacy

Indicators	Ineffective group (n=23)	Effective group (n=102)	χ^2	P
Sex			0.280	0.597
Male	12 (52.17)	47 (46.08)		
Female	11 (47.83)	55 (53.92)		
Age (years old)			3.484	0.062
≥45	16 (69.57)	49 (48.04)		
<45	7 (30.43)	53 (51.96)		
BMI (kg/m^2)			2.488	0.115
≥22	18 (78.26)	62 (60.78)		
<22	5 (21.74)	40 (39.22)		
Course of disease (weeks)			5.697	0.017
≥5	20 (86.96)	62 (60.78)		
<5	3 (13.04)	40 (39.22)		
Hypertension			5.297	0.021
With	6 (26.09)	9 (8.82)		
Without	17 (73.91)	93 (91.18)		
Diabetes			5.738	0.017
With	8 (34.78)	14 (13.73)		
Without	15 (65.22)	88 (86.27)		
Hyperlipidemia			14.371	<0.001
With	12 (52.17)	16 (15.69)		
Without	11 (47.83)	86 (84.31)		
Therapeutic method			7.583	0.006
Lactulose oral solution	17 (73.91)	43 (42.16)		
Lactulose oral solution combined with Macrogol 4000 Powder	6 (26.09)	59 (57.84)		

Note: BMI, body mass index.

Table 4. Assignment table

Variables	Assignment
Course of disease (weeks)	≥5=1, <5=0
Hypertension	With =1, without =0
Diabetes	With =1, without =0
Hyperlipidemia	With =1, without =0
Therapeutic method	Lactulose oral solution =1, lactulose oral solution combined with Macrogol 4000 Powder =0.

significant decrease in the research group (P<0.05). See **Figure 2** for details.

The two groups were comparable in adverse reactions

The number of cases with diarrhea, abdominal distension, abdominal pain, nausea and vomiting were observed and counted. There was no remarkable difference in the incidence of total adverse reactions between the two groups (P=0.451). See **Table 6**.

The research group exhibited a more advantageous improvement in serum indexes

Serum indexes were tested in both groups. Before treatment, the SS levels in the control and research group were (17.47 ± 3.27) pg/mL and (18.14 ± 2.94) pg/mL, respectively, which reduced to (14.20 ± 2.91) pg/mL and (9.20 ± 2.65) pg/mL after treatment, respectively. Concerning the NO levels in the control group and the research group, they were (80.83 ± 11.78) mmol/L and (83.43 ± 10.63) mmol/L prior to treatment, and (65.25 ± 10.29) mmol/L and (56.35 ± 6.08) mmol/L after treatment, respectively. The SP levels in the control and research group were (30.37 ± 4.86) pg/mL and (31.31 ± 5.57) pg/mL before treatment, and (39.33 ± 6.17) pg/mL and (44.57 ± 7.00) pg/mL after treatment, respectively. It can be seen that there were no remark-

Table 5. Multivariate analysis of factors affecting efficacy

Variables	β	SE	Wald	P	Exp (β)	95% CI
Course of disease (weeks)	2.410	0.831	8.418	0.004	11.130	2.186-56.682
Hypertension	2.200	0.816	7.263	0.007	9.025	1.822-44.700
Diabetes	2.460	0.800	9.445	0.002	11.705	2.438-56.195
Hyperlipidemia	2.305	0.668	11.910	0.001	10.022	2.707-37.107
Therapeutic method	1.255	0.610	4.233	0.040	3.508	1.061-11.596

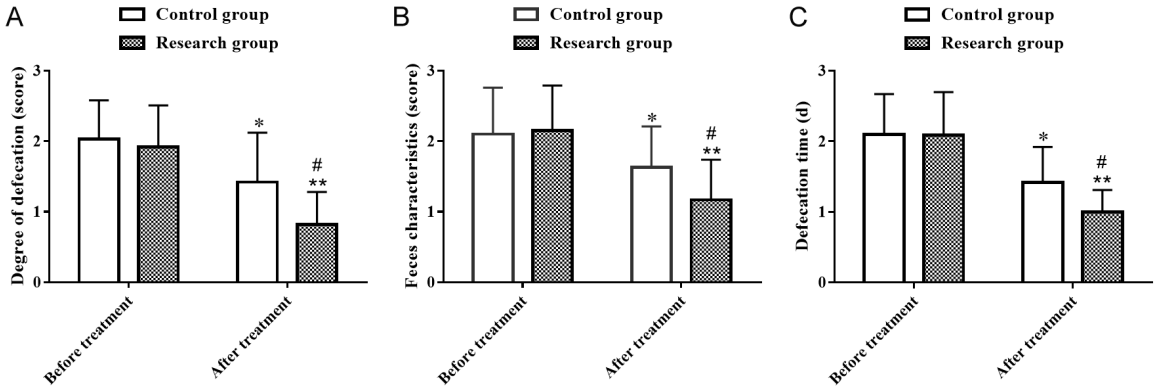

Figure 1. Difficulty degree of defecation, stool trait, and time of defecation in both groups. A: Comparison of difficulty degree of defecation before and after treatment between groups; B: Comparison of stool trait between groups before and after treatment; C: Comparison of defecation time between groups before and after treatment. Note: *P<0.05 and **P<0.01 represent comparison with before treatment; #P<0.05 represents comparison with the control group after treatment.

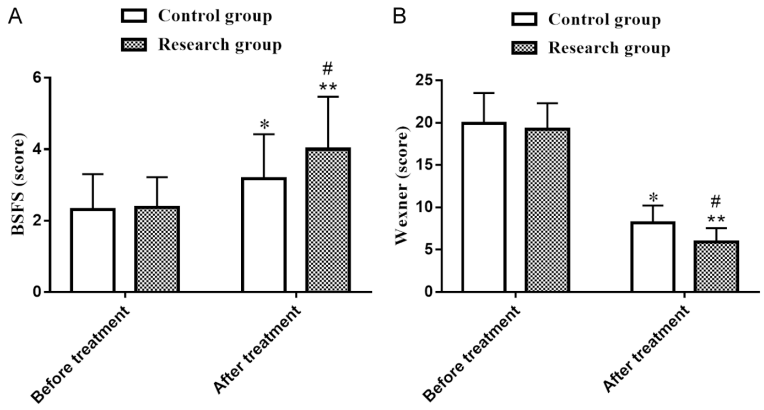

Figure 2. BSFS and Wexner Constipation Scale scores. A: Comparison of BSFS scores between two groups before and after treatment. B: Comparison of Wexner Constipation Scale scores before and after treatment between two groups. Note: *P<0.05 and **P<0.01 represent comparison with before treatment; #P<0.05 represents comparison with the control group after treatment. BSFS, Bristol Stool Form Scale.

able differences in the levels of SS, NO, and SP before treatment (P>0.05), and that SS and NO appeared to be reduced while SP increased after treatment (P<0.05). Moreover, the research group demonstrated lower levels of SS and NO, as well as higher SP levels compared to the control group (P<0.05). See **Figure 3**.

The research group experienced a superior quality of life

The quality of life of both groups was assessed by the PAC-QOL scale. The PAC-QOL scores in the control and research groups before treatment were (86.67 ± 7.39) points and (85.12 ± 8.21) points, respectively, which decreased to (55.15 ± 7.48) points and (39.98 ± 5.61) points after treatment. The results indicated that the total PAC-QOL scores were not significantly different before the treatment (P>0.05). While after treatment, the total PAC-QOL scores decreased significantly in both groups, and the research group showed lower total PAC-QOL scores compared to the control group. See **Figure 4**.

Table 6. Comparison of adverse reactions between groups

Indexes	Control group (n=60)	Research group (n=65)	χ^2/t	P
Diarrhea	3 (5.00)	2 (3.08)		
Abdominal distension	2 (3.33)	1 (1.54)		
Abdominal pain	0 (0.00)	1 (1.54)		
Nausea and vomiting	2 (3.33)	1 (1.54)		
Total	7 (11.67)	5 (7.69)	0.568	0.451

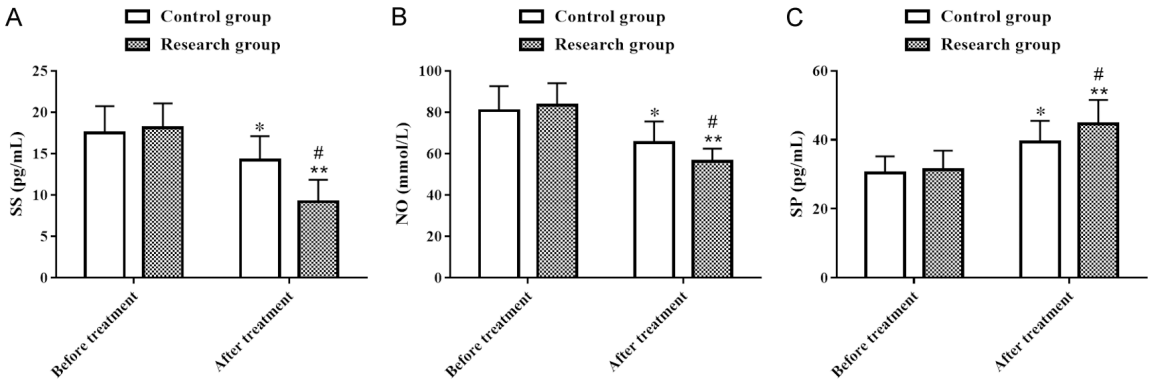

Figure 3. SS, NO, and SP levels in both groups. A: Comparison of SS levels between groups before and after treatment; B: Comparison of NO levels between groups before and after treatment; C: Comparison of SP levels between groups before and after treatment. Note: *P<0.05 and **P<0.01 represent comparison with before treatment; #P<0.05 represents comparison with the control group after treatment. SS, somatostatin; NO, nitric oxide; SP, substance P.

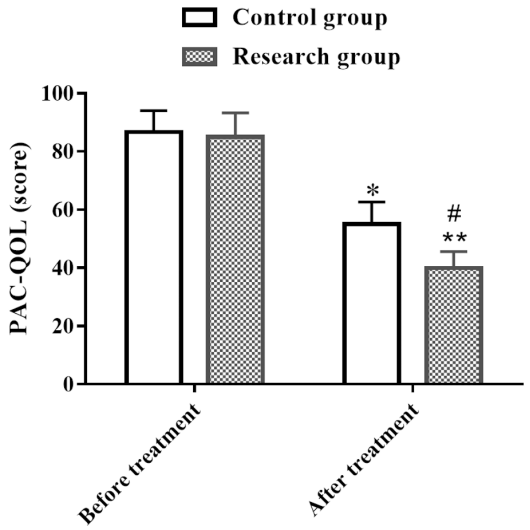

Figure 4. Comparison of PAC-QOL scores before and after treatment in both groups. Note: *P<0.05 and **P<0.01 represent comparison with before treatment; #P<0.05 represents comparison with the control group after treatment. PAC-QOL, Patient Assessment of Constipation Quality of Life.

Discussion

In this study, FC patients treated with lactulose oral solution combined with Macrogol 4000 Powder exhibited better efficacy (90.77% vs. 71.67%), which suggests that the combination treatment can achieve superior therapeutic efficacy, and significantly alleviate the symptoms of the patients. This is related to the fact that Macrogol 4000, as an osmotic laxative, can increase the water content of feces via its osmotic action in the intestine, thereby achieving a laxative treatment effect [24]. Treepongkaruna et al. [25] reported that Macrogol 4000 Powder was more suitable for chronic constipation in young children compared to lactulose oral solution, with a comparable safety profile but higher efficacy, significantly increasing stool frequency and improving stool consistency and bowel patency, which is similar to the results of our study. Subsequently, this study further found that the course of disease, hypertension, diabetes, hyperlipidemia, and

therapeutic method significantly affect the efficacy in FC patients. Namely, patients with a course of disease ≥5 weeks, hypertension, diabetes, and hyperlipidemia may be at higher risk of ineffective treatment, and treatment strategies should be reevaluated. This may be due to the fact that FC patients with a disease course of ≥5 weeks generally have more severe conditions and are relatively more difficult to treat. Moreover, FC patients with comorbid hypertension, diabetes, or hyperlipidemia are affected by the underlying diseases, which may impede the full extent of the curative effect of the combined intervention regimen.

Better symptom recovery was also identified in FC patients treated with lactulose oral solution combined with Macrogol 4000 Powder. This may be attributed to the fact that Macrogol 4000 Powder can combine with water molecules through hydrogen bonds to prevent the intestine from absorbing water molecules in feces, thereby softening the feces and making them less prone to dryness and easier to excrete, while promoting intestinal peristalsis and increasing the patient's body's defecation urge [26]. A study by Lyseng-Williamson et al. [13] indicated that Macrogol 4000 Powder was more conducive to improving stool frequency and consistency compared with lactulose, which was related to its effect on reducing vomiting and flatulence, similar to the results of our study. Furthermore, this study found the combination of lactulose oral solution and Macrogol 4000 Powder was more beneficial for ameliorating fecal traits and disease severity in patients with FC. According to a report by Li et al. [27], Macrogol 4000 in patients with maternal constipation was shown to significantly downgrade the WCS score compared to lactulose at weeks 1 and 2 of treatment, resulting in a faster treatment effect, supporting our findings. A meta-analysis by Fang et al. [28] has also reported that Macrogol 4000 combined with fecal microbiota transplantation for the treatment of adult FC can significantly upregulate BSFS scores, which is similar to our findings. This is partly due to the improvement of intestinal motility by Macrogol 4000, thereby alleviating the condition. Regarding safety, the combination of lactulose oral solution and Macrogol 4000 Powder showed a good safety profile without significantly increasing the risk of adverse reactions. This may be related to the fact that both medications are not absorbed into the bloodstream by the intestines, and that Macrogol 4000 Powder does not interfere with the normal physiological processes of other substances in the intestine [29]. Mínguez et al. [30] found that Macrogol 4000 Powder was more effective in treating FC patients compared to placebo, possessing a high safety and tolerability profile, which is similar to our findings. Our results further showed that lactulose oral solution combined with Macrogol 4000 Powder in FC patients down-regulated the abnormally elevated levels of SS and NO, as well as up-regulated the abnormally low levels of SP. It is known that abnormal levels of SS, NO, and SP are all closely associated with insufficient intestinal motility in the body, and are significantly related to the development and progression of FC. Among them, SS and NO are risk factors for intestinal hyperdynamics, with the former negatively affecting the body's intestinal dynamics by inhibiting the release of acetylcholine and the latter inhibiting gastrointestinal peristalsis by impeding smooth muscle movement. Whereas SP is a facilitator of intestinal peristalsis, with its mechanism of facilitation associated with stimulation of neurons in the intestinal wall [31, 32]. In a study by Zhang et al. [33], the soluble dietary fiber of hawthorn relieved constipation symptoms by down-regulating the levels of inhibitory hormones such as SS and NO and up-regulating the expression of excitatory hormones like SP, which is consistent with the results of our study. To a certain extent, this also reflects how the treatment of FC with lactulose oral solution combined with Macrogol 4000 powder may achieve therapeutic effects by enhancing the body's intestinal motility, promoting the release of acetylcholine, and stimulating the neurons of the intestinal wall. Finally, lactulose oral solution combined with Macrogol 4000 Powder helped to improve the quality of life in FC patients. This may be related to the faster recovery of symptoms and the more significantly improved stool quality and constipation severity in the research group, which is helpful in restoring a normal life, thereby improving their quality of life. In a study by Piche et al. [34], lactulose plus paraffin significantly improved PAC-QOL scores compared with polyethylene glycol for the treatment of FC, which is similar to our findings.

This study has several limitations that need to be addressed. First, this study only included adult FC patients, which limits the universality

of the research results. Second, for the identified risk factors, further subgroup analysis is needed in the future to explore the heterogeneity and verify our conclusions. Third, in view of the lack of exploration of relevant treatment mechanisms, basic experiments are required for relevant mechanism analysis in future studies, which will contribute to further research on treatment targets. In future research, children with FC can also be included for analysis.

Conclusion

Our findings suggest that lactulose oral solution combined with Macrogol 4000 Powder for FC patients is conducive to improving efficacy, facilitating symptomatic recovery, and ameliorating the constipated condition while ensuring safety. The combination regimen can positively regulate the abnormal serum levels of SS, NO, and SP, and improve quality of life. In addition, patients with the following characteristics may face a greater risk of ineffective treatment, that is, a course of disease ≥5 weeks, hypertension, diabetes, and hyperlipidemia. Moreover, we recommend the use of lactulose oral solution combined with Macrogol 4000 Powder for superior efficacy.

Disclosure of conflict of interest

None.

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References

[1] Sharma A, Rao SSC, Kearns K, Orleck KD and Waldman SA. Review article: diagnosis, management and patient perspectives of the spectrum of constipation disorders. Aliment Pharmacol Ther 2021; 53: 1250-1267.

[2] Lv CL, Song GQ, Liu J, Wang W, Huang YZ, Wang B, Tian JS, Yin MQ and Yu Y. Colorectal motility patterns and psychiatric traits in functional constipation and constipation-predominant irritable bowel syndrome: a study from China. World J Gastroenterol 2023; 29: 5657-5667.

[3] Wlodarczyk J, Wasniewska A, Fichna J, Dziki A, Dziki L and Wlodarczyk M. Current overview on clinical management of chronic constipation. J Clin Med 2021; 10: 1738.

[4] Leung AK and Hon KL. Paediatrics: how to manage functional constipation. Drugs Context 2021; 10: 2020-11-2.

[5] Arco S, Saldana E, Serra-Prat M, Palomera E, Ribas Y, Font S, Clave P and Mundet L. Functional constipation in older adults: prevalence, clinical symptoms and subtypes, association with frailty, and impact on quality of life. Gerontology 2022; 68: 397-406.

[6] Werth BL and Christopher SA. Potential risk factors for constipation in the community. World J Gastroenterol 2021; 27: 2795-2817.

[7] Shin JE, Jung HK, Lee TH, Jo Y, Lee H, Song KH, Hong SN, Lim HC, Lee SJ, Chung SS, Lee JS, Rhee PL, Lee KJ, Choi SC and Shin ES; Clinical Management Guideline Group under the Korean Society of Neurogastroenterology and Motility. Guidelines for the diagnosis and treatment of chronic functional constipation in Korea, 2015 revised edition. J Neurogastroenterol Motil 2016; 22: 383-411.

[8] de Geus A, Koppen IJN, Flint RB, Benninga MA and Tabbers MM. An update of pharmacological management in children with functional constipation. Paediatr Drugs 2023; 25: 343-358.

[9] Kang SJ, Cho YS, Lee TH, Kim SE, Ryu HS, Kim JW, Park SY, Lee YJ and Shin JE; Constipation Research Group of the Korean Society of Neurogastroenterology and Motility. Medical management of constipation in elderly patients: systematic review. J Neurogastroenterol Motil 2021; 27: 495-512.

[10] Cha RR, Park SY and Camilleri M; Constipation Research Group of Korean Society of Neurogastroenterology and Motility. Constipation in patients with chronic kidney disease. J Neurogastroenterol Motil 2023; 29: 428-435.

[11] Pieber TR, Svehlikova E, Mursic I, Esterl T, Wargenau M, Sartorius T, Pauly L, Schwejda-Guettes S, Neumann A, Faerber V, Stover JF, Gaigg B and Kuchinka-Koch A. Blood glucose response after oral lactulose intake in type 2 diabetic individuals. World J Diabetes 2021; 12: 893-907.

[12] Meng S, Pan Y, Deng Q, Wang L and Chang Q. Efficacy and safety of lactulose on the treatment of puerperal constipation. Zhonghua Yi Xue Za Zhi 2015; 95: 2288-2290.

[13] Lyseng-Williamson KA. Macrogol (polyethylene glycol) 4000 without electrolytes in the symptomatic treatment of chronic constipation: a profile of its use. Drugs Ther Perspect 2018; 34: 300-310.

[14] Gaci N, Chaudhary PP, Tottey W, Alric M and Brugere JF. Functional amplification and preservation of human gut microbiota. Microb Ecol Health Dis 2017; 28: 1308070.

[15] Bekkali NLH, Hoekman DR, Liem O, Bongers MEJ, van Wijk MP, Zegers B, Pelleboer RA, Ver-

wijs W, Koot BGP, Voropaiev M and Benninga MA. Polyethylene glycol 3350 with electrolytes versus polyethylene glycol 4000 for constipation: a randomized, controlled trial. J Pediatr Gastroenterol Nutr 2018; 66: 10-15.

[16] Abe T, Kunimoto M, Hachiro Y, Ohara K, Inagaki M, Hishiyama H and Murakami M. Tolerance and efficacy of polyethylene glycol 4000 in elderly patients with chronic constipation: a retrospective, single-center, observational study. J Anus Rectum Colon 2021; 5: 291-296.

[17] Aziz I, Whitehead WE, Palsson OS, Tornblom H and Simren M. An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. Expert Rev Gastroenterol Hepatol 2020; 14: 39-46.

[18] Lee HY, Kwon OJ, Kim JE, Kim M, Kim AR, Park HJ, Cho JH, Kim JH and Choi SM. Efficacy and safety of acupuncture for functional constipation: a randomised, sham-controlled pilot trial. BMC Complement Altern Med 2018; 18: 186.

[19] Lim YJ, Rosita J, Chieng JY and Hazizi AS. The prevalence and symptoms characteristic of functional constipation using rome iii diagnostic criteria among tertiary education students. PLoS One 2016; 11: e0167243.

[20] Liu T, He S, Li Q and Wang H. Cap-assisted endoscopic sclerotherapy is effective for rectal mucosal prolapse associated outlet obstructive constipation. Arab J Gastroenterol 2023; 24: 85-90.

[21] Bharucha AE, Chakraborty S and Sletten CD. Common functional gastroenterological disorders associated with abdominal pain. Mayo Clin Proc 2016; 91: 1118-1132.

[22] Zhou J, Cheng G, Pang H, Liu Q and Liu Y. The effect of 131I-induced hypothyroidism on the levels of nitric oxide (NO), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-alpha), total nitric oxide synthase (NOS) activity, and expression of NOS isoforms in rats. Bosn J Basic Med Sci 2018; 18: 305-312.

[23] Hamaguchi S, Varma MG, Nakagawa H, Ozaka A, Shimizu S, Maeshibu T, Wakita T, Green J and Fukuhara S. Translation and validation testing of the constipation-related quality of life scale for use in Japan. Cureus 2023; 15: e48661.

[24] Fordtran JS and Hofmann AF. Seventy years of polyethylene glycols in gastroenterology: the journey of PEG 4000 and 3350 from nonabsorbable marker to colonoscopy preparation to osmotic laxative. Gastroenterology 2017; 152: 675-680.

[25] Treepongkaruna S, Simakachorn N, Pienvichit P, Varavithya W, Tongpenyai Y, Garnier P and Mathiex-Fortunet H. A randomised, double-blind study of polyethylene glycol 4000 and lactulose in the treatment of constipation in children. BMC Pediatr 2014; 14: 153.

[26] Poulsen JL, Brock C, Olesen AE, Nilsson M and Drewes AM. Clinical potential of naloxegol in the management of opioid-induced bowel dysfunction. Clin Exp Gastroenterol 2014; 7: 345-358.

[27] Li H, Zhang P and Xue Y. A comparison of the safety and efficacy of polyethylene glycol 4000 and lactulose for the treatment of constipation in pregnant women: a randomized controlled clinical study. Ann Palliat Med 2020; 9: 3785-3792.

[28] Fang S, Wu S, Ji L, Fan Y, Wang X and Yang K. The combined therapy of fecal microbiota transplantation and laxatives for functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2021; 100: e25390.

[29] Fang S, Song Y, Liu Y and Wang L. Randomized clinical trial: efficacy and tolerability of two different split dose of low-volume polyethylene glycol electrolytes for bowel preparation before colonoscopy in hospitalized children. Pediatr Res 2021; 90: 171-175.

[30] Minguez M, Lopez Higueras A and Judez J. Use of polyethylene glycol in functional constipation and fecal impaction. Rev Esp Enferm Dig 2016; 108: 790-806.

[31] Zhang W, Lyu M, Bessman NJ, Xie Z, Arifuzzaman M, Yano H, Parkhurst CN, Chu C, Zhou L, Putzel GG, Li TT, Jin WB and Zhou J; JRI Live Cell Bank; Hu H, Tsou AM, Guo CJ and Artis D. Gut-innervating nociceptors regulate the intestinal microbiota to promote tissue protection. Cell 2022; 185: 4170-4189, e4120.

[32] Arslan B, Dogan G, Orenay-Boyacioglu S, Caliskan M and Elevli M. Serotonin, ghrelin, and motilin gene/receptor/transporter polymorphisms in childhood functional constipation. Rev Assoc Med Bras (1992) 2023; 69: 279-284.

[33] Zhang H, Zu Q, Zhang J, Liu S, Zhang G, Chang X and Li X. Soluble dietary fiber of hawthorn relieves constipation induced by loperamide hydrochloride by improving intestinal flora and inflammation, thereby regulating the aquaporin ion pathway in mice. Foods 2024; 13: 2220.

[34] Piche T and Dapoigny M. Comparative efficacy and safety of lactulose plus paraffin vs polyethylene glycol in functional constipation: a randomised clinical study. United European Gastroenterol J 2020; 8: 923-932.