Clinical Trial/Experimental Study

Medicine®

OPEN

Lactulose for the treatment of Chinese children with chronic constipation

A randomized controlled trial

Yuan Cao, MB[a], Shi-ming Liu, MB[b,*]

Abstract

Background: This study aimed to investigate the efficacy and safety of lactulose for the treatment of Chinese children with chronic constipation.

Methods: A total of 100 children with chronic constipation were included in this randomized controlled trial. They were equally and randomly allocated to a treatment group (n=50) and a placebo group (n=50). The participants in the treatment group received lactulose, while the subjects in the placebo group received placebo intervention. The children in both groups were treated for a total of 6 weeks. The primary outcome was daily stool frequency. The secondary outcomes consisted of stool consistency, measured by the Bristol Stool Form Scale, abdominal pain, flatulence, as well as the adverse events. All outcomes were measured at baseline and after 6-weeks treatment.

Results: After 6 weeks treatment, lactulose showed better outcomes in daily stool frequency ($P < .01$), and stool consistency ($P < .01$), except the abdominal pain ($P = .24$), and flatulence ($P = .44$), compared with the placebo. Additionally, no significant differences regarding all adverse events were detected between 2 groups.

Conclusion: The results of this study found that lactulose is efficacious for Chinese children with chronic constipation after 6-weeks of treatment.

Abbreviations: ITT = intention-to-treat , SAS = statistical analysis system.

Keywords: constipation, efficacy, lactulose, safety

1. Introduction

Constipation is a very common gastrointestinal condition in childhood.[1–3] It has been estimated that the prevalence of such condition ranges from 3% of all visits to pediatric outpatient clinics to 25% of all visits to pediatric gastroenterologists in USA.[1,3–5] The other study reported that the median prevalence is 8.9%, varying from 0.7% to 29.6%.[3,6] In China, its prevalence rates were reported as 24.9% in Shanghai, and 29.6% in Hong Kong.[7–8]

Chronic constipation in children can often result in significant abdominal pain, poor appetite, school absenteeism, or even depression for children with such condition, which significantly affect the quality of their life, as well as their families.[9–10] Thus, producing soft and painless stools help to prevent such condition.[10]

Various modalities are utilized to treat chronic constipation. These managements consist of high fiber diet, toilet training, and behavioral therapy, as well as the medication, including the stimulant laxatives (lactulose, polyethylene glycol solution), and lubricants.[11–20] Of these, lactulose is recommended as one of the most potential candidates for this condition control.[21–23] However, there is still insufficient evidence of lactulose for Chinese children with chronic constipation. Therefore, this study explored the efficacy and safety of lactulose for the management of Chinese children with chronic constipation.

2. Methods/design

2.1. Ethical approval

This study was approved by the ethics committee of Yulin No. 2 Hospital and The People's Hospital of Yan'an.

2.2. Study design

It was conducted at Yulin No. 2 Hospital and The People's Hospital of Yan'an from April 2016 to March 2018. A total of 100 eligible children with chronic constipation were included in this randomized controlled trial. They were equally divided into the treatment group and the placebo group, each group 50 participants. The patients in the treatment group received lactulose, while the subjects in the placebo group were given placebo intervention. Patients in both groups were treated for a total of 6 weeks. All primary and secondary outcomes were measured at baseline and after 6 weeks treatment in this study.

Editor: Daryle Wane.

The authors have no conflicts of interest to disclose.

[a] Department of Pharmacy, Yulin No. 2 Hospital, Yulin, [b] Department of Health Materials, Yan'an People's Hospital, Yan'an, Shaanxi, China.

[*] Correspondence: Shi-ming Liu, Department of Health Materials, Yan'an People's Hospital, No. 57 Qilipu St, Baota Qu, Yan'an, Shaanxi, 716000, China (e-mail: shiming2011012@yeah.net).

Medicine (2018) 97:52(e13794)

Received: 16 October 2018 / Accepted: 30 November 2018

http://dx.doi.org/10.1097/MD.0000000000013794

2.3. Patients

Patients inclusion criteria dictated that,

1. all included children aged between 2 and 6 years old with a diagnosis of chronic functional constipation (experienced at least 3 months) according to the modification of the Rome II criteria for preschool children ;[24]
2. fulfill at least 2 of the following 4 criteria: a stool frequency < 3 times weekly for at least 3 months, or fecal incontinence (children who had already acquired toilet skills) ≥2 times weekly for at least 3 months, at least 1 periodic passage of large amount stool every 7 to 30 days, or a palpable mass at abdomen or rectum;
3. written informed consent was obtained from guardians of each child.

Exclusion criteria included children with organic causes of defecation disorders, suspected gastrointestinal obstruction, abdominal or rectal surgery that might affect the constipation, or any other conditions that cause the chronic constipation, or previously used lactulose or other laxatives, or prebiotics or probiotics or antibiotics 1 month before the study. In addition, children were also excluded if they had severe neurologic or psychiatric, or mental disorders.

2.4. Randomization

A total of 100 children were randomly divided into the treatment group and the placebo group at a ratio of 1:1, each group 50 children. Randomization schedule was conducted by using of sequential numbers, generating from the statistical analysis system (SAS) package 8.1 (SAS Institute Inc., Cary, NC, USA). Any randomization and allocation information were concealed in opaque sealed envelopes. The patients, investigators, outcome assessors, and data analysts were masked to the treatment allocation information.

2.5. Intervention schedule

Patients in the treatment group received 5 ml lactulose (3.3 g) daily for a total of 6 weeks. The participants in the placebo group underwent placebo, the same size, dose, color, flavor, and appearance as the lactulose in the treatment group. Additionally, subjects in the placebo group also received a total of 6 weeks placebo.

2.6. Outcome measurements

The primary outcome was daily stool frequency. The secondary outcome measurements included stool consistency, measured by the Bristol Stool Form Scale (from 1, hard stools; to 7, liquid stools)[25]; abdominal pain (from 0, not at all; to 3, continuous); flatulence (from 0, not at all; to 3, continuous). In addition, any adverse events were also recorded in this study. All outcomes were evaluated at baseline and after 6 weeks of treatment.

3. Statistical analysis

The data analysis was conducted by using the SAS package 8.1 (SAS Institute Inc., Cary, NC, USA). The sample size was calculated based on the difference in mean stool frequency of 40% between lactulose and placebo, with $\alpha = 0.5$, $\beta = 0.8$. Assuming a 20% drop-out rate, the required sample size of the present study was therefore estimated to be 100 children, with 50 assigned to each group.

All data were analyzed by intention-to-treat (ITT) analysis. The Mann–Whitney U test or t test was applied to analyze the continuous data. The Pearson chi-square test or Fisher exact test was utilized to analyze the categorical data. The statistical significance level was defined as $P < .05$.

4. Results

In total, 148 children with chronic constipation were assessed for eligibility in this study (Fig. 1). Of these, 48 subjects were excluded. Thus, 100 children were randomly allocated to the treatment group (n = 50), and the placebo group (n = 50). Nine children withdrew from the study because of the lost to follow-up, and consent withdrawn, although all patients entered into the final analysis by using ITT approach.

The baseline characteristics of all included patients in both groups are shown in Table 1. There were no significant differences in all baseline characteristics between 2 groups.

After 6-weeks treatment, patients in the treatment group did exert better outcomes in daily stool frequency ($P < .01$, Table 2), and stool consistency ($P < .01$, Table 3), compared with patients in the control group. On the other hand, no significant differences in abdominal pain ($P = .24$, Table 4), and flatulence ($P = .44$, Table 5) were found between 2 groups after the 6-week treatment.

During the 6-week treatment period, no severe adverse events were recorded (Table 6). No death related to the treatment was documented. No significant differences of all adverse events were detected between 2 groups.

5. Discussion

Several previous trials have explored the efficacy and safety of lactulose in children with chronic constipation, and have achieved encouraging outcome results.[26–28] However, all these trials were conducted among the children population from other countries, but not for Chinese children. To our best knowledge, the present randomized controlled trial firstly specifically investigated the efficacy and safety of lactulose in Chinese children with chronic constipation.

The results of the present study showed that lactulose contributed to better treatment outcomes against chronic constipation in Chinese children after 6-weeks of treatment compared with the placebo. Our findings demonstrated the promising efficacy and fairly safety of lactulose for treating Chinese children with chronic constipation.

In the present randomized controlled trial, the primary outcome was daily stool frequency. The secondary outcomes were measured by the stool consistency, abdominal pain, flatulence, and adverse events. After 6-week of treatment, lactulose showed statistically significant increase in the change of mean daily stool frequency ($P < .01$), and stool consistency ($P < .01$), compared with the placebo. Moreover, no severe adverse events were detected in lactulose group, and both groups had similar safety profile. These results indicated the promising efficacy of lactulose for treating Chinese children with chronic constipation with safety profile.

The present study has 2 limitations. First, the shortcoming of this study was the missing further follow-up evaluation after the 6-week treatment stopped. Indeed, follow-up of either short- or long-term efficacy of lactulose for the treatment in Chinese children with chronic constipation is still needed to be explored. Second, this study did not evaluate the comprehensive conditions

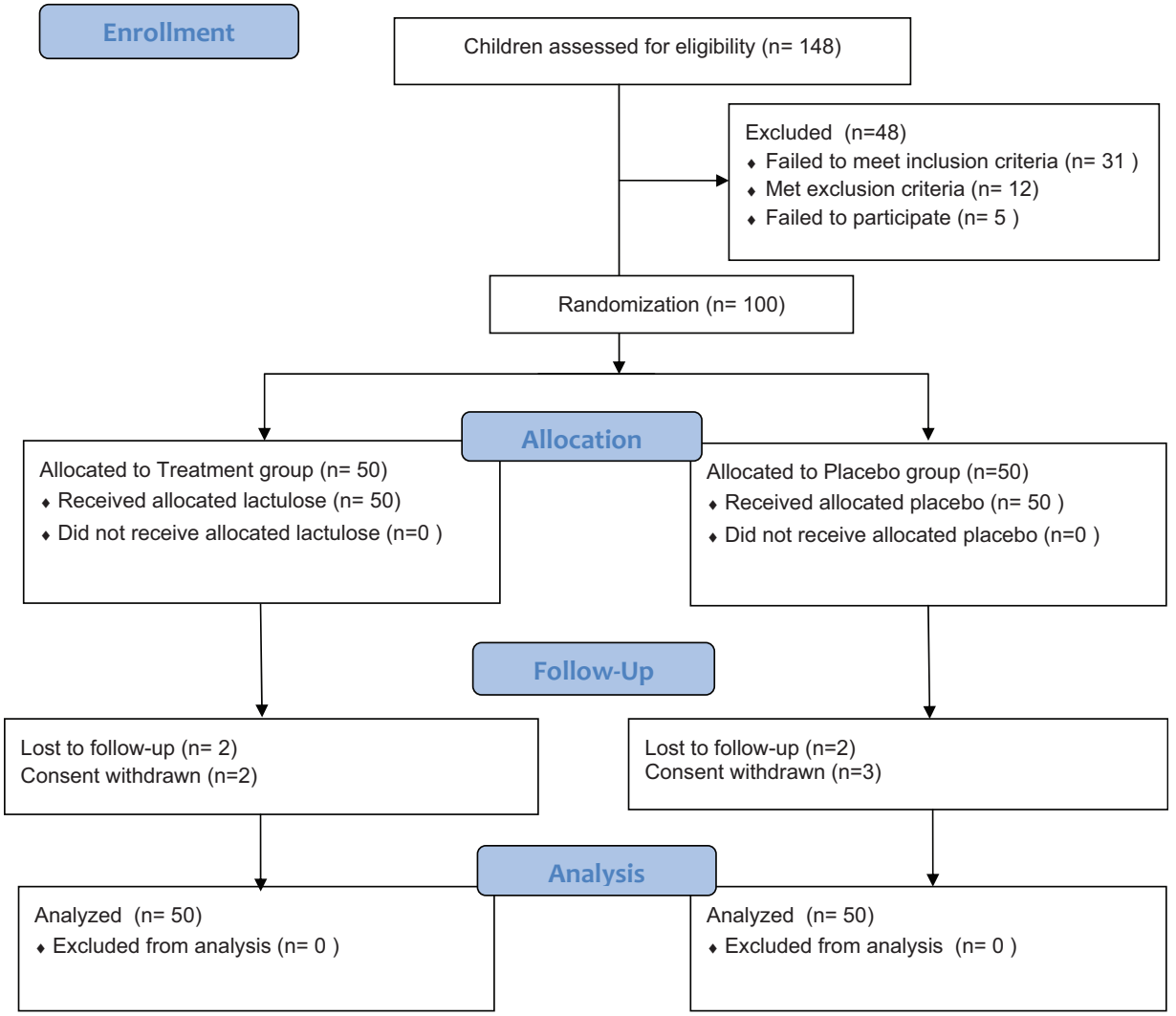

Figure 1. Patients flowchart through the study.

Table 1

Comparison of baseline characteristics.

Characteristics	Treatment group (n = 50)	Placebo group (n = 50)	*P* value
Mean age (year)	3.9 (0.6)	4.0 (0.7)	.44
Gender			
Boys	28 (56.0)	26 (52.0)	.69
Girls	22 (44.0)	24 (48.0)	–
Race (China)			
Han Ethnicity	45 (90.0)	47 (94.0)	.47
Hui Ethnicity	5 (10.0)	3 (6.0)	–
Duration of chronic constipation (week)	39.2 (16.7)	40.4 (17.5)	.73
Previous treatment	41 (82.0)	38 (76.0)	.46

Data are present as mean ± standard deviation or number (%).

Table 2

Comparison stool frequency between 2 groups.

Stool frequency	Treatment group (n = 50)	Placebo group (n = 50)	*P* value
Baseline	0.6 (0.5)	0.7 (0.6)	.37
Change from baseline	0.5 (0.3, 0.8)	0.2 (0.1, 0.6)	
Difference between groups		0.4 (0.2, 0.7)	<.01

Mean ± standard deviation (range).

Table 3

Comparison of stool consistency between 2 groups.

Bristol stool form scale	Treatment group (n = 50)	Placebo group (n = 50)	*P* value
Baseline	3.0 (1.1)	3.1 (1.2)	.56
Difference from treatment before	1.6 (0.9, 2.3)	0.5 (0.2, 0.9)	
Difference between groups		1.1 (0.6, 1.7)	<.01

Data are present as mean ± standard deviation (range).

Table 4

Comparison of abdominal pain between 2 groups.

Abdominal pain	Treatment group (n = 50)	Placebo group (n = 50)	*P* value
Before treatment	1.6 (0.7)	1.7 (0.7)	.48
Difference from treatment before	−0.2 (−0.5, −0.1)	−0.1 (−0.3, −0.1)	
Difference between groups		−0.1 (−0.2, −0.1)	.24

Data are present as mean ± standard deviation (range).

Table 5

Comparison of flatulence between 2 groups.

Flatulence	Treatment group (n = 50)	Placebo group (n = 50)	*P* value
Before treatment	1.6 (0.9)	1.7 (0.8)	.56
Difference from treatment before	0.4 (0.1, 0.6)	0.3 (0.1, 0.5)	
Difference between groups		0.1 (0.1, 0.3)	.44

Data are present as mean ± standard deviation (range).

Table 6

Comparison of adverse events between 2 groups.

Adverse events	Treatment group (n = 50)	Placebo group (n = 50)	*P* value
Anal dilation	11 (22.0)	8 (16.0)	.45
Upper respiratory tract infections	8 (16.0)	6 (13.0)	.57
Faecaloma	9 (18.0)	6 (13.0)	.40
Anal fissure	7 (14.0)	5 (10.0)	.54
Hard faeces	4 (8.0)	2 (4.0)	.41
Rhinorrhoea	1 (2.0)	2 (4.0)	.57

Data are present as number (%).

of the subjects did, such as the quality of life, and psychological outcomes.

6. Conclusions

This study found that lactulose can treat Chinese children with chronic constipation effectively and safety. Future studies with longer-term treatment and follow-up evaluation are still needed to be explored.

Author contributions

Conceptualization: Shi-ming Liu and Yuan Cao.
Data curation: Shi-ming Liu and Yuan Cao.
Formal analysis: Yuan Cao.
Investigation: Shi-ming Liu.
Methodology: Yuan Cao.
Project administration: Shi-ming Liu.
Resources: Shi-ming Liu.
Software: Yuan Cao.
Supervision: Shi-ming Liu.
Validation: Shi-ming Liu and Yuan Cao.
Visualization: Shi-ming Liu and Yuan Cao.
Writing – original draft: Shi-ming Liu and Yuan Cao.
Writing – review & editing: Shi-ming Liu and Yuan Cao.

References

[1] Tabbers MM, Boluyt N, Berger MY, et al. Clinical practice. Eur J Pediatr 2011;170:955–63.
[2] Yanitskaya MY, Sapozhnikov VG. Diagnostic possibilities of hydrocolonic echography at chronic constipation in children. Eksp Klin Gastroenterol 2015;1:36–47.
[3] van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. Am J Gastroenterol 2006;101:2401–9.
[4] Loening-Baucke V. Chronic constipation in children. Gastroenterology 1993;105:1557–64.
[5] Taitz LS, Wales JK, Urwin OM, et al. Factors associated with outcome in management of defecation disorders. Arch Dis Child 1986;61:472–7.
[6] Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best Pract Res Clin Gastroenterol 2011;25:3–18.

[7] Ip KS, Lee WT, Chan JS, et al. A community-based study of the prevalence of constipation in young children and the role of dietary fibre. Hong Kong Med J 2005;11:431–6.
[8] Zhou H, Yao M, Cheng GY, et al. Prevalence and associated factors of functional gastrointestinal disorders and bowel habits in Chinese adolescents: a school-based study. J Pediatr Gastroenterol Nutr 2011;53:168–73.
[9] Belsey J, Greenfield S, Candy D, et al. Systematic review: impact of constipation on quality of life in adults and children. Aliment Pharmacol Ther 2010;31:938–49.
[10] Rowan-Legg A. Managing functional constipation in children. Paediatr Child Health 2011;16:661–70.
[11] Olness K, Tobin JSr. Chronic constipation in children: can it be managed by diet alone? Postgrad Med 1982;72:149–54.
[12] Bustos Fernández LM, Prizont R, Soifer LO. A controlled pilot study on the efficacy of a low dose antibiotic for the treatment of chronic constipation in patients receiving a high fiber diet. Acta Gastroenterol Latinoam 2013;43:275–8.
[13] Agarwal J. Chronic constipation. Indian J Pediatr 2013;80:1021–5.
[14] Loening-Baucke V. Management of chronic constipation in infants and toddlers. Am Fam Physician 1994;49:397–400.
[15] Ghoshal UC. Chronic constipation in Rome IV era: the Indian perspective. Indian J Gastroenterol 2017;36:163–73.
[16] Chiarioni G. Biofeedback treatment of chronic constipation: myths and misconceptions. Tech Coloproctol 2016;20:611–8.
[17] Vitton V, Damon H, Benezech A, et al. Clinical practice guidelines from the French National Society of Coloproctology in treating chronic constipation. Eur J Gastroenterol Hepatol 2018;30:357–63.
[18] Liu LW. Chronic constipation: current treatment options. Can J Gastroenterol 2011;25(Suppl B):22B–8B.
[19] Brenner DM. Stimulant laxatives for the treatment of chronic constipation: is it time to change the paradigm? Gastroenterology 2012;142:402–4.
[20] Gálvez Castillo C, Garrigues Gil V. Functional gastrointestinal disorders. What type of laxative should be used in patients with chronic constipation? What are the indications for irritant laxatives? Gastroenterol Hepatol 2008;31:614–5.
[21] Maydeo A. Lactitol or lactulose in the treatment of chronic constipation: result of a systematic. J Indian Med Assoc 2010;108:789–92.
[22] Ejerskov Pedersen C, Jønsson IM, Siggaard C, et al. Treatment of chronic constipation in children. Ugeskr Laeger 2013;175:1855–8.
[23] Bu LN, Chang MH, Ni YH, et al. Lactobacillus casei rhamnosus Lcr35 in children with chronic constipation. Pediatr Int 2007;49:485–90.
[24] Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. Gut 1999;45:I60–8.
[25] Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920–4.
[26] Connolly P, Hughes IW, Ryan G. Comparison of "Duphalac" and "irritant" laxatives during and after treatment of chronic constipation: a preliminary study. Curr Med Res Opin 1974-1975;2:620–5.
[27] Romańczuk W, Korczowski R. Duphalac (lactulose) in the treatment of chronic constipation in children. Wiad Lek 1995;48:96–9.
[28] Gremse DA, Hixon J, Crutchfield A. Comparison of polyethylene glycol 3350 and lactulose for treatment of chronic constipation in children. Clin Pediatr (Phila) 2002;41:225–9.