Study Protocol Systematic Review

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Efficacy and safety of lactulose for the treatment of irritable bowel syndrome

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Abstract

Background: In this study, investigators will evaluate the efficacy and safety of lactulose for the treatment of irritable bowel syndrome (IBS).

Methods: Literature search for relevant studies up to present will be conducted in MEDICINE, EMBASE, Google Scholar, Web of Science, Cochrane Library, Wangfang, Allied and Complementary Medicine Database, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure. The included studies are randomized controlled trials of lactulose in patients with IBS. We will use RevMan 5.3 software using statistical analysis.

Results: This study will provide a high-quality integration of current evidence of lactulose for treating IBS on several aspects including global IBS symptoms, abdominal pain, defecation urgency, stool frequency, stool consistency, quality of life, and adverse events.

Conclusions: This study will provide the evidence for the clinical efficacy and safety of lactulose for the treatment of IBS.

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Abbreviations: IBS = irritable bowel syndrome, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis, RCTs = randomized controlled trials.

Keywords: efficacy, irritable bowel syndrome, lactulose, randomized controlled trial, safety

1. Introduction

Irritable bowel syndrome (IBS) is a very common and functional gastrointestinal disease.[1–3] It is diagnosed based on symptoms and is characterized by recurrent abdominal pain and discomfort, excess gas, diarrhea or constipation, and stool pattern.[4–6] It has been estimated that the prevalence of IBS is about 5% to 22% among general population experiencing IBS,[7] and such number is about 5% to 10% in China.[8–10] Its incidence presents a persistently increasing tread.[11–13] Thus, it is very important to treat this disorder effectively. Fortunately, several studies have reported that lactulose has been widely utilized for the treatment of IBS.[14–18] However, its efficacy for IBS is still inconclusive, and no study has been addressed this issue. Therefore, this study will systematically assess the efficacy and safety of lactulose for the treatment of patients with IBS.

2. Methods

2.1. Study selection criteria

2.1.1. Types of studies. This study will include all randomized controlled trials (RCTs) of lactulose for the treatment of IBS without publication status. However, other studies will be excluded, such as animal studies, case studies, and non-RCTs.

2.1.2. Types of interventions. The experimental treatments must be any forms of lactulose.

The control therapies can be any interventions, except lactulose.

2.1.3. Types of patients. Regardless of any limitations of race, sex, age, and economic status, the patients diagnosed as IBS will be included.

2.1.4. Types of outcome measurements. The outcomes consist of global IBS symptoms; abdominal pain; defecation urgency; stool frequency; stool consistency, as measured by Bristol score; quality of life, as measured by Short Form-36 Health Survey; and adverse events.

2.2. Search strategy

The following databases will be searched up to the present: Cochrane Library, MEDICINE, EMBASE, Google Scholar, Web of Science, Wangfang, Allied and Complementary Medicine Database, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure. We will also search other

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The authors report no conflicts of interest.

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Table 1

Search strategy details for Cochrane Library.

Number	Search terms
1	Mesh descriptor: (Irritable Bowel Syndromes) explode all trees
2	((Syndrome *) or (Irritable Bowel*) or (Colon*) or (Irritable Colon*) or (Colitis, Mucous*) or (Mucous Colitis*)):ti, ab, kw
3	Or 1–2
4	Mesh descriptor: (Lactulose) explode all trees
5	((Kristalose*) or (Constulose*) or (Enulose*) or (Generlac*)):ti, ab, kw
6	Or 4–5
7	MeSH descriptor: (Randomized controlled trials) explode all trees
8	MeSH descriptor: (Clinical trials as topic) explode all trees
9	((Random*) or (Randomly*) or ((Clinical study*) or (Allocation*) or (Placebo*) or (Blind*) or (Trial*) or (RCTs*) or (Controlled study*)):ti, ab, kw
10	Or 7–9
11	3 and 6 and 10

literature records, such as trial registry, dissertations, and conference proceedings. The search strategies designed for Cochrane Library are presented in Table 1. Similar modified search strategies will be applied to the other databases. No language limitation will be imposed.

2.3. Data collection and analysis

2.3.1. Study selection. All studies searched by both electronic databases and grey literature. Two investigators will independently scan the titles, abstracts, and records of all the studies to explore more potential studies according to the previous defined eligibility criteria. All disagreements will be solved by a consensus and discussion with the help of a third investigator. The reasons excluding studies will be recorded and presented in the flowchart.

2.3.2. Data extraction. Two investigators will independently extract data and fill the standard data extraction sheet, which will consist of study information, such as first author, publication year, study design, study methods, treatment details, outcomes, safety, and follow-up details. All different opinions between 2 investigators will be solved via consensus and discussion. A third arbiter will be invited to reach an agreement.

2.3.3. Missing data dealing with. In case of missing or unclear data, we will try to contact original authors through obtain sufficient data. Despite such attempts, if we cannot obtain the data, it will be performed based on the intent-to-treat principle.

2.3.4. Risk of bias assessment. Two investigators will assess the risk of bias based on the Cochrane risk of bias tool. This tool includes seven aspects, and each assessment outcome will be showed via 1 of the 3 types: low, unclear, and high risk of bias. All disagreements will be solved by a consensus and discussion between 2 investigators, and if necessary, the third investigator will intervene.

2.3.5. Methods of treatment measurements. Dichotomous data will be assessed via risk ratio and 95% confidence intervals, and continuous data will be expressed through mean difference or standardized mean difference and 95% confidence intervals.

2.3.6. Heterogeneity assessment. We will use I^2 statistics to evaluate the heterogeneity. $I^2 \leq 50\%$ indicates acceptable heterogeneity, while $I^2 > 50\%$ means significant heterogeneity.

2.3.7. Assessment of reporting bias. If the analysis consists of more than 10 RCTs, we will conduct funnel plot and Egger regression test to assess the publication bias or small-study effects.[19,20]

2.4. Data synthesis

RevMan 5.3 software will be utilized to perform statistical analysis. If the heterogeneity is acceptable ($I^2 \leq 50\%$), a fixed-effect model and meta-analysis will be applied. If the heterogeneity is substantial ($I^2 > 50\%$), a random-effect model will be performed, and subgroup analysis will be carried out to identify possible reasons for such high heterogeneity. This study will not pool the data if there is still significant heterogeneity after subgroup analysis. Outcome results will be reported as narrative summary.

2.4.1. Subgroup analysis. To explore the potential sources of heterogeneity, we will carry out subgroup analysis according to the different characteristics, interventions, and outcome measurements.

2.4.2. Sensitivity analysis. Sensitivity analysis will be conducted to assess the robustness of pooled outcome results by removing studies with high risk of bias.

3. Discussion

Several previous studies have explored the efficacy and safety of lactulose for the treatment of IBS. However, to the best of our knowledge, this study will be the first one to comprehensively assess current available treatments through quantitative methods. The results of this study will provide information on the credibility current evidence and research directions for patients, physicians, and clinical researchers.

3.1. Ethics and dissemination

The expected goal is disseminating this study at peer reviewed publication. The ethical approval is not inquired in this study, because no participants' privacy will not be involved.

Author contributions

Conceptualization: Hong-bin Chen, Xiao-ying Su.
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Formal analysis: Hong-bin Chen.
Funding acquisition: Xiao-ying Su.
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References

[1] Kim JH, Jee SR. Irritable bowel syndrome. Korean J Gastroenterol 2019;73:84–91.
[2] Kavanagh RG, O'Grady J, Carey BW, et al. Review of the role of abdominal imaging in irritable bowel syndrome. World J Radiol 2018;10:143–9.
[3] Adriani A, Ribaldone DG, Astegiano M, et al. Irritable bowel syndrome: the clinical approach. Panminerva Med 2018;60:213–22.
[4] Usai-Satta P, Bellini M, Lai M, et al. Therapeutic approach for irritable bowel syndrome: old and new strategies. Curr Clin Pharmacol 2018;13:164–72.
[5] Defrees DN, Bailey J. Irritable bowel syndrome: epidemiology, pathophysiology, diagnosis, and treatment. Prim Care 2017;44:655–71.
[6] Gwee KA, Ghoshal UC, Chen M. Irritable bowel syndrome in Asia: pathogenesis, natural history, epidemiology, and management. J Gastroenterol Hepatol 2018;33:99–110.
[7] Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol 2012;10: 712–21.
[8] Liu J, Hou X. A review of the irritable bowel syndrome investigation on epidemiology, pathogenesis and pathophysiology in China. J Gastroenterol Hepatol 2011;26(Suppl 3):88–93.
[9] Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clin Epidemiol 2014;6:71–80.
[10] Sperber AD, Dumitrascu D, Fukudo S, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. Gut 2017;66:1075–82.
[11] Soares RL. Irritable bowel syndrome: a clinical review. World J Gastroenterol 2014;20:12144–60.
[12] Pan CH, Chang CC, Su CT, et al. Trends in irritable bowel syndrome incidence among Taiwanese adults during 2003–2013: a population-based study of sex and age differences. PLoS One 2016;11:e0166922.
[13] Dai C, Jiang M. The incidence and risk factors of post-infectious irritable bowel syndrome: a meta-analysis. Hepatogastroenterology 2012;59: 67–72.
[14] Tuteja AK, Talley NJ, Stoddard GJ, et al. Double-blind placebo-controlled study of rifaximin and lactulose hydrogen breath test in gulf war veterans with irritable bowel syndrome. Dig Dis Sci 2019;64:838–45.
[15] Bae S, Lee KJ, Kim YS, et al. Determination of rifaximin treatment period according to lactulose breath test values in nonconstipated irritable bowel syndrome subjects. J Korean Med Sci 2015;30:757–62.
[16] Le Nevé B, Posserud I, Böhn L, et al. A combined nutrient and lactulose challenge test allows symptom-based clustering of patients with irritable bowel syndrome. Am J Gastroenterol 2013;108:786–95.
[17] Park JS, Yu JH, Lim HC, et al. Usefulness of lactulose breath test for the prediction of small intestinal bacterial overgrowth in irritable bowel syndrome. Korean J Gastroenterol 2010;56:242–8.
[18] Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. a double-blind, randomized, placebo-controlled study. Am J Gastroenterol 2003;98:412–9.
[19] Sutton AJ, Duval SJ, Tweedie RL, et al. Empirical assessment of effect of publication bias on meta-analyses. BMJ 2000;320:1574–7.
[20] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.