Placebo response rate in patients with chronic constipation: a protocol for systematic review

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Abstract
Objective: The aim of this systematic review and meta-analysis is to calculate the pooled placebo response rate in patients with chronic constipation (CC) in randomized controlled trial (RCT) and its related factors.

Method: This systematic review and meta-analysis will be conducted under the guidance of Cochrane Handbook. The inclusive and exclusive criteria and search strategies for PubMed, Cochrane Library, and Embase will be introduced in this protocol. Data collection, extraction, and assessment of risk of bias will be conducted independently by 2 reviewers. The pooled placebo response rate and its 95% confidence interval (95%CI) will be calculated and the heterogeneity assessment, publication bias assessment, and subgroup analysis will be performed using R 3.6.0. This study has been registered on the PROSPERO platform (CRD42019121287).

Result: The results of this systematic review and meta-analysis will be published in a peer-reviewed journal.

Abbreviations: CC = chronic constipation, CI = confidence interval, IBS-C = irritable bowel syndrome with predominant constipation, MeSH = medical subject headings, RCT = randomized controlled trial.

Keywords: chronic constipation, meta-analysis protocol, placebo response rate

1. Introduction

Chronic constipation is a recurrent functional bowel disorder. The prevalence was estimated around 14% worldwide.[1-5] Although not life threatening, it can cause the decline of patients' quality of life and bring a heavy burden to the health service system.[6,7] A large amount of clinical trials were conducted; however, the efficacy was still unsatisfied.[8-10] Therefore, further exploring for new management remains necessary.

As it is known that most of the therapeutic randomized controlled trials (RCTs) use the placebo or sham treatment as control group, and the therapeutic effect is demonstrated through the comparison of 2 or more groups. That means placebo response rate is essential during the efficacy evaluation process for most of the therapeutic clinical trials. However, there is no article yet has reported and analysis the fact that the placebo response rate in constipated patients varies from 7% to 71%.[4,11-14]

Furthermore, placebo response rate is one of the necessary parameters in sample size calculation, which is of vital importance during the design of clinical trials. Taking the 2 RCT conducted by Ziegenhagen and Kruis[15] and Harish et al[16] for example, both of which failed to demonstrate the statistical difference between treatment group and control group. And both authors pointed out in the article that the small sample size limited the detection of an actual therapeutic effect. In fact, appropriate sample size can not only prevent the RCT studies from the low power to detect the true difference between groups, but also prevent the waste of time, money, and resources and the delay in introducing new drug.[17,18]

Thus, we conduct this systematic review and meta-analysis to calculate the pooled placebo response rate in patients with chronic constipation (CC) and to discuss how different characteristics in the clinical trials might affect it. This meta-analysis has been registered with ID number CRD42019121287 on the PROSPERO International Prospective Register of systematic reviews.

2. Methods

2.1. Study selection

2.1.1. Inclusive criteria.

a. Randomized controlled trials or crossover designed;

b. Adults (participants aged >16 years old);

c. Diagnosis of chronic constipation, functional constipation, or IBS with predominant constipation (IBS-C) based on the

Abstract

OR constipation[MeSH Terms] OR Dyschezia[Title/Abstract] OR chronic constipation[Title/Abstract] OR constipation[Title/Abstract] NOT humans[MeSH Terms]

Abstract

randomly[Title/Abstract] OR trial[Title/Abstract] OR placebo[Title/Abstract] OR drug therapy[MeSH Terms] OR clinical trial[Publication Type] OR randomized[Title/Abstract]

#1 randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR drug therapy[MeSH Terms] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR trial[Title/Abstract] OR trial[Title/Abstract]

2.1.2. Exclusive criteria.

a. Participants in the study have constipation induced by drugs, organic diseases of digestive tract, or other systemic diseases, which are confirmed by obvious and definite evidence (e.g., the result of an endoscopy, biopsy, laboratory tests, etc).

2.1.3. Outcome measurement.

After a period of treatment, placebo response rates were calculated according to patient-reported information or using questionnaires based on Rome criteria and designed at the beginning of every RCT trials. The global improvement is defined as patients reporting for overall improvement or experiencing 2 or more aspects of the following symptoms:

a. increase in bowel movement;

b. reduced frequency of hard or lumpy stools;

c. reduced frequency of straining;

d. improvement of the sense of incomplete evacuation;

e. improvement of the feeling of anorectal blockage;

f. decrease of the need for digital manoeuvres to assist defecation;

g. improvement in abdominal pain (for IBS-C only).

The primary outcome is the placebo response rate for global improvement. The additional outcome is the placebo response rate for one of the above improvements.

2.2. Records retrieve

PubMed, Cochrane Library, Embase will be electronically searched from their inception to December 12, 2019 with no restriction of publication dates and languages. The search strategy will include both the medical subject headings (MeSH) terms and the keywords that describe the intervention (placebo, sham stimulation), characteristics of participants (chronic constipation, functional constipation, IBS-C, Fecal Impaction, Colonic Inertia), and randomized controlled trials.

2.2.1. Search strategy for PubMed.

#1 randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR drug therapy[MeSH Terms] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR trial[Title/Abstract]

#2 animals[MeSH Terms] NOT humans[MeSH Terms]

#3 #1 NOT #2

#4 chronic constipation[Title/Abstract] OR constipation[Title/Abstract] OR constipation[MeSH Terms] OR Dyschezia[Title/Abstract] OR Colonic Inertia[Title/Abstract] OR Fecal Impaction

[Title/Abstract] OR impacted stool[Title/Abstract] OR lumpy stool[Title/Abstract] OR rock like stool[Title/Abstract]

#5 opioid[Title] OR cancer[Title] OR carcinoma[Title]

#6 child[Title] OR children[Title] OR childhood[Title]

#7 #3 AND #4 NOT #5 NOT #6

2.2.2. Search strategy for Embase (accessed via OVID).

- randomized controlled trial.mp. or exp randomized controlled trial/

- (random* or factorial* or crossover* or placebo*).ab.

- 1 or 2

- chronic constipation.mp. or exp constipation/ or exp chronic constipation/

- limit 4 to (human and(adult 18–64 years) or aged <65+ years))

- 3 and 5

2.2.3. Search strategy for Cochrane.

#1 MeSH descriptor: [Randomized Controlled Trial] explode all trees

#2 randomized controlled trial in Trials (Word variations have been searched)

#3 #1 OR #2

#4 MeSH descriptor: [Constipation]explode all trees

#5 constipation in Trials (Word variations have been searched)

#6 #4 OR #5

#7 MeSH descriptor: [Placebos]explode all trees

#8 placebo in Trials (Word variations have been searched)

#9 #7 OR #8

#10 #3 AND #6 AND #9

2.3. Data collection

2.3.1. Screening for eligible records. Using the search strategies as stated above, the records retrieve will be conducted independently by 2 reviewers (JC and XL) according to the Cochrane Handbook. Then 2 reviewers will independently screen both titles and abstracts for eligibility based on the inclusive and exclusive criteria described in Section 2.1. The records management is performed using EndNote X9. The detail information about this procedure will be summarized in the form of a PRISMA flow diagram.

2.3.2. Data extraction and assessment of risk of bias. Full text of each eligible articles will be viewed and the related data will be extracted by 2 reviewers (JC and XL) independently according to the Cochrane Handbook. The 5-scale Jadad score (2 points for randomization, 2 points for Double blinding, and 1 point for Drop-outs or withdrawals) and the statement of allocation concealment will be used to assess the quality and the risk of bias of each studies.[19,20] Any differences emerged during this procedure will be discussed by the 2 reviewers (JC and XL). If no consensus is reached, then an independent reviewer (TB) will be consulted for further solution. The data needed to be extracted includes: year, geographical location, number of centers, criteria used to define chronic constipation, active treatment, duration of therapy, dosing schedule, sample size, placebo response rate (%), etc.
2.3.3. Deal with missing data. We would retrieve manuscripts from publishers, supplementary documents, corresponding records on ClinicalTrials.gov or contact the author for original data, if the experimental data were found to be inadequate or missing. Inadequate data would be excluded if original data cannot be retrieved.

2.4. Statistical analysis

2.4.1. Data synthesis and heterogeneity assessment. All studies that meet the inclusion criteria and have complete data will be incorporated into the final data synthesis process. R 3.6.0 will be used to conduct all the statistical analysis, first we will calculate the pooled placebo response rate and its 95% confidence interval (95%CI) and draw the forest plot. Then the heterogeneity among all the included studies will be assessed using the $I^2$ statistic. If it is not appropriate to conduct meta-analysis, we will then perform a systematic review only.

2.4.2. Publication bias assessment. Funnel plot will be drawn to evaluate the publication bias visually, and after that the Trim and Fill of the funnel plot will be conducted if necessary. The specific test, such as Egger’s test and Begg’s test will also be conducted to provide more exact evidence for publication bias.[21,22]

2.4.3. Subgroup analysis and meta-regression. If significant heterogeneity were found ($I^2 > 50\%$), the subgroup analysis and meta-regression would be performed to seek the potential reason that may cause the heterogeneity.

2.4.4. Confidence in cumulative evidence. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)[23] will be used to assess the strength of the cumulative evidence independently by 2 reviewers (JC and XL). The quality of evidence (very low, low, moderate, or high) will be assessed according to the following considerations: risk of bias, consistency, directness, and publication bias.

3. Discussion

The placebo response rate not only acts as a standard comparative index for most of the therapeutic clinical trials, but also has significant influence on the design of RCT studies. However, the placebo response rate in constipated patients has not been fully studied based on numerous data in clinical trials. We designed the first systematic review and meta-analysis to report the pooled placebo response rate in patients with chronic constipation.

Through this study, we will obtain the size of the pooled placebo response rate and its 95%CI, as well as how it varies with different characteristics in clinical trials. Compared with the placebo response rate reported in RCT, the pooled placebo response rate obtained in this study can maintain the inadequate power in original RCTs caused by small sample size. And this may provide some references for later therapeutic clinical trials for constipation. Although the top position of systematic review and meta-analysis in the evidence pyramid has been questioned in recent years, it is no doubt that this statistical method plays a crucial role in exploring evidence based on considerable original studies.[24,25] This protocol is reported under PRISMA-P.[26]

Author contributions

Tao Bai and Xiaohua Hou developed the main idea of this study. Jie Chen developed the search strategy. Jie Chen and Xinghuang Liu will finish all the selection of studies, data extraction, the assessment of the risk of bias, and data synthesis. The disagreements between Jie Chen and Xinghuang Liu will be arbitrated by Tao Bai. Jie Chen drafted the original manuscript of the protocol, which was revised by Tao Bai. All authors have read and approved the final manuscript of the protocol.

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