Rikkunshito for Upper Gastrointestinal Syndrome in Patients With Cancer: A Systematic Review and Meta-analysis Protocol

Hong Liu
Chengdu University of Traditional Chinese Medicine
Yifeng Ren
Chengdu University of Traditional Chinese Medicine Affiliated Hospital
Yuting Wang
Chengdu University of Traditional Chinese Medicine Affiliated Hospital
Yu Yang
Chengdu University of Traditional Chinese Medicine Wenjiang Campus: Chengdu University of Traditional Chinese Medicine
Chuan Zheng
Chengdu University of Traditional Chinese Medicine Affiliated Hospital
Fengming You (yfmdoc@163.com)
Chengdu University of Traditional Chinese Medicine https://orcid.org/0000-0001-7900-4060

Protocol

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Abstract

Background

Upper gastrointestinal syndrome including nausea, vomiting, and anorexia is a common side effect of chemotherapy, which are associated with treatment interruptions, reduced food intake, decreased functionality and a worse quality of life. Rikkunshito is a traditional herbal medicine that has gained increasing attention in recent years for its effect on relieving gastrointestinal disorders in various digestive diseases, while its efficacy for upper gastrointestinal syndrome induced by chemotherapy remains uncertain.

Methods

Databases including PubMed, EMBASE, MEDLINE, Cochrane Library, Chinese databases, and Japanese database will be systematically searched from their inception onwards. Randomized controlled trials will be assessed. The primary outcome parameters are the complete control (CC) rate, complete response (CR) rate, and complete protection (CP) rate in the overall phase (0–120 hours). The secondary outcomes include: (I) the CC rate, CR rate and CP rate during the acute phase (0–24 hours) and delayed phase (24–120 hours); (II) the score and frequency of vomiting, nausea, and anorexia occurring; (III) the daily dietary intake and body weight; (IV) plasma ghrelin level; (V) quality of life; (VI) incidence of adverse events. The overall quality of the data will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation guidelines. Risk of bias will be evaluated by the Cochrane tool. Reporting bias will be estimated using Begg and Egger tests. Heterogeneity will be evaluated by the I^2 statistic and Q test. If $I^2 > 50\%$, sensitivity analysis and subgroup analysis of different items will be performed.

Discussion

From the study, we will ascertain the efficacy and safety of rikkunshito in chemotherapy-induced upper gastrointestinal syndrome. This review may provide evidence for rikkunshito as an adjuvant to treat upper gastrointestinal symptoms in patients with cancer.

Systematic review registration

CRD42020214299 in PROSPERO.

Background

Upper gastrointestinal (GI) syndrome including nausea, vomiting, and anorexia, is commonly seen in patients with cancer, especially those undergoing chemotherapy. Chemotherapy-induced nausea and vomiting (CINV) has been estimated to be as high as 70%-80% in patients receiving chemotherapies without appropriate antiemetic prophylaxis(1). Patients also experience appetite loss when chemotherapy, which is also known as chemotherapy-induced anorexia (CIA), even though the antiemetic combination therapy has clearly decreased the incidence of CINV(2). The failure in prevention and

treatment of CINV and CIA may cause cessation in chemotherapy, which further potentiated poor treatment outcomes. Moreover, persistent upper gastrointestinal symptoms increase the risk of dehydration, electrolyte imbalance and malnutrition, which strongly impair the quality of life (QOL) and survival of patients(3). Therefore, CINV and CIA control is the key point for successful completion of chemotherapy and QOL maintenance.

Despite advances in prophylactic antiemetics, the symptoms still cannot be completely controlled. CINV typically presents in two phases depending on the onset timing of vomiting: acute CINV occurs within 24h after chemotherapy administration, whereas delayed CINV presents within 24h-120h period after chemotherapy administration (4). Therapeutically, the acute CINV is well managed with serotonin type 3 (5-HT_3) receptor antagonist (5, 6). While in different circumstances, to prevent the delayed CINV, the 5-HT_3 receptor antagonist, NK-1 receptor antagonist, and dexamethasone use alone or in combination in a presentive manner from before starting the chemotherapy, but it is not well controlled as compared with the acute CINV (7). When it comes to CIA, the problem gets trickier as any promising drugs that specifically target anorexia have not yet developed. To complete chemotherapy while maintaining the patient's QOL, it is desirable to establish a convenient and effective treatment method.

Rikkunshito (TJ-43), a traditional Japanese medicine, also known as Liu-Jun-Zi-Tang in China and Yukgunja-tang (YGJT) in Korea, has been extensively prescribed in East Asian countries to treat GI disorders, including functional dyspepsia, gastritis, gastroesophageal reflux disease(8-10), and also common adverse events by drugs and surgical interventions (11, 12). Rikkunshito comprises eight raw herbs in the following doses: *Atractylodes Lancea Rhizome* 4.0 g*, Poria Sclerotium* 4.0 g*, Pinellia Tuber* 4.0 g*, Ginseng* 4.0 g*, Jujube* 2.0 g*, Citrus Unshiu Peel* 2.0 g*, Glycyrrhiza* 1.0 g*, and Ginger* 0.5 g(13). Up to now, there have been a few reports where rikkunshito was administered in combination with antiemetic drugs against emesis and anorexia during emetogenic chemotherapy (12, 14-19). Some preclinical studies have also found an appetite stimulation ability of rikkunshito and clarified that it was the flavonoids in rikkunshito antagonized 5-HT2B/2C receptors that suppressed the decrease in plasma acylated ghrelin levels(20, 21). Ghrelin, a small peptide hormone secreted from the stomach which enhanced food intake(22), it can alleviate CINV and CIA(23).

However, the efficacy and safety of rikkunshito for upper GI syndrome induced by chemotherapy remains uncertain because such related clinical findings are inconsistent. According to the Shunsuke Ohnishi, Myung-Hyun Ko, and Junichi Seike's report(12, 14, 15), the add-on treatment with rikkunshito provided an additive efficacy against CINV and CIA, especially during the delayed phase, while it did not show any additional benefits in Toshiyuki Harada's report(16). A systematic review and meta-analysis of the effect of rikkunshito on upper GI syndrome was published before(24),while the researchers also drew an ambiguous conclusion. They included patients suffering from upper GI symptoms regardless of the causative diseases, nevertheless, a subgroup analysis for patients with cancer was not performed. Obviously, the upper GI syndrome related to cancer or cancer therapies was more severe, persistent, and distressing than functional digestive diseases(25, 26). What's more, several new clinical trials were published in recent years; hence, there is need for a review to summarize and evaluate the efficacy of

rikkunshito on upper GI syndrome in patients with cancer and its effect on dietary intake, bodyweight, ghrelin secretion, and quality of life.

Methods/design

This systematic review and meta-analysis is registered at the International Prospective Register of Systematic Reviews (number CRD42020214299) and will be performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines(27).

Search strategy

A systematic search will be executed in the following electronic databases from their inception onwards: PubMed, EMBASE, MEDLINE, Cochrane Library, Chinese databases [Chinese National Knowledge Infrastructure and Wan-Fang database], and Japanese database [National Institute of Informatics], with language limitations to English, Chinese and Japanese. Gray articles, reference lists of articles and related journals were searched manually in Google Scholar. The search strategy is shown in the **Supplementary Table 1.**

Study selection

Guided by the Cochrane Back Review Group(28), the study selection process will be carried out independently by two reviewers. Preliminary screening of studies will be performed by scanning the titles and abstracts of reports to identify studies meeting the inclusion criteria and to exclude obviously irrelevant studies. Then, the full texts of the remaining studies will be assessed to determine the eligible studies for meta-analysis. Duplicate publications will be identified and excluded by checking the publication year, names of the all authors, study design, characteristics of participants and outcome results. After the selection, the gray relevant studies will be obtained by checking the reference lists of the included studies. Any discrepancies will be resolved by consensus.

Eligibility criteria

Studies will be selected according to the following items: type of studies, participants, interventions, outcome measures.

Studies Design

Randomized controlled trials (RCTs) in parallel or cross over-design are available. For cross-over trials, we will analyze the data before the cross-over. The following literary types will not be considered: non-randomized controlled trials (non-RCTs), retrospective study, case reports, reviews, protocols, editorials, letters, and commentaries.

Participants

The review will consider the studies those recruited adult participants (aged ≥ 18 years) pathologically diagnosed as cancer receiving chemotherapy especially moderate-emetic-risk chemotherapy (MEC) and high-emetic-risk chemotherapy (HEC).

Interventions and comparators

Rikkunshito was often added to corticosteroid, NK-1 receptor antagonist, 5-HT_3 receptor antagonist and other antiemetic agents, so the studies comparing the efficacy of standard antiemetic therapies with and without the addition of oral administration of rikkunshito will be evaluated.

Outcome measures

The primary outcome parameters are the complete control (CC; i.e., no emesis, no rescue medication, and no significant nausea) rate, complete response (CR; i.e., no emesis, no rescue medication) rate, and complete protection (CP; i.e., no emesis, no significant nausea, and no recue medication) rate in the overall phase (0–120 hours).

The secondary outcomes include: (I) the CC rate, CR rate and CP rate during the acute phase (0–24 hours) and delayed phase (24–120 hours); (II) the score and frequency of vomiting, nausea, and anorexia occurred; (III) the daily dietary intake and body weight; (IV) plasma ghrelin level; (V) quality of life; (VI) incidence of adverse events.

Data extraction and management

Extracted data will be obtained independently by two investigators using a standardized electronic data extraction sheet. If the study were designed as a crossover trial, the first cycle will be preferred. The captured information will be stored and managed in Microsoft Office Excel 2019 (Microsoft Corporation, Redmond, WA, USA). If the data were missing, ambiguous or presented in a form that cannot be extracted, the corresponding author will be contacted for additional information and clarification.

The following data will be extracted:

(I) Basic information: authors, publication date, country, language

(II) Methodology: study design, trial size, participant's characteristics (size and gender, cancer types and stages, the doses, and durations of chemotherapeutic drugs), intervention (the dose and duration of rikkunshito), risk of bias information.

(III) Outcomes: the measures and intergroup differences in upper gastrointestinal symptoms scores, dietary intake, plasma ghrelin level, quality of life, incidence rate of drug-related side effects.

Measures of treatment effects

Data reported in graphical form will be derived by GetData Graph Digitizer Software (GetData Pty Ltd., Kogarah, Australia). The original data, which were presented as the median and interquartile range, will be converted to the mean and standard deviation (SD) using the methods described by Wan et al(29). Data will be synthesized using Review Manager 5.3. The mean difference (MD) or standard mean difference (SMD) will be used to measure the therapeutic effect with 95% confidence interval (CI) for continuous data, while risk ratios (RRs) with 95% CIs will be calculated for dichotomous outcomes. The continuity correction will be applied for zero event studies. All *P*-values are two-sided and a *P* value of <0.05 indicates statistical significance.

Assessment of evidence quality

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be utilized to grade the quality of evidence (30) by two reviewers. In terms of the five GRADE criteria, that is, the risk of bias, inconsistency, indirectness, imprecision, and publication bias, the evidence quality of each study will be ranked as high, moderate, low, or very low. GRADEprofiler (GRADEpro) software will be applied to generate the Summary of findings table (www.gradepro.org).

Assessment of risk of bias

RCTs meeting the inclusion criteria will be evaluated for risk of bias using the Cochrane Collaboration's tool across six domains (selection, performance, detection, attrition, reporting, and other). Risk of bias for each domain will be categorized as low, unclear, or high and two investigators will independently complete the 'risk of bias' chart form of each study. Any disagreements will be resolved by a discussion between the two reviewers or a third reviewer will adjudicate if necessary.

Assessment of publication bias

The funnel plot will be estimated using Begg and Egger tests in order to check the publication bias if more than ten studies are included (31, 32). A one-sided $P < 0.05$ indicates a significant publication bias, and the trim-and-fill computation will be applied to to further assess the potential effects of publication bias.

Heterogeneity, sensitivity, and subgroup analysis

Heterogeneity will be assessed using I^2 statistics. I^2 <50% indicates insignificant heterogeneity, and fixed-effects models will be used. Otherwise, random effects models will be applied if there is a level of heterogeneity, and a sensitivity and subgroup analysis will be adopted for exploring the sources of heterogeneity. The sensitivity analysis will be mainly carried out to evaluate the robustness of the meta-analysis results and will be conducted by excluding the study in which the quality was rated as 'high risk'. The analysis will be repeated after omitting the low-quality studies. Subgroup analysis will be conducted according to the dose and duration of rikkunshito, the emetogenicity of chemotherapy, if necessary and possible.

Discussion

Cancer patients are increasingly seeking nonconventional modalities to complement their cancer care, especially in symptom control. Rikkunshito has been offered to effectively treat the digestive tract symptoms (33), especially in relieving nausea/vomiting and improving nausea (23, 34). While the usefulness of rikkunshito in managing the chemotherapies-induced digestive tract symptoms remains unknown.

This systematic review and meta-analysis will retrospectively synthesize and consolidate evidence on the administration of rikkunshito to upper GI symptoms on patients with cancer. This in return may provide a complementary prevention for chemotherapy-induced upper GI symptoms control.

Abbreviations

CC: Complete control; CR: Complete response; CP: Complete protection; GI: Gastrointestinal; CINV: Chemotherapy-induced nausea and vomiting; CIA: Chemotherapy-induced anorexia; QOL: Quality of life; RCTs: Randomized controlled trials; non-RCTs: Non-randomized controlled trials; MEC: Emetic-risk chemotherapy; HEC: High-emetic-risk chemotherapy; SD: Standard deviation; MD: Mean difference; SMD: Standard mean difference; RR: Risk ratio; CI: Confidence interval; GRADE: Grading of Recommendation, Assessment, Development and Evaluation.

Declarations

Ethics approval and consent to participate

Ethical approval is not required, as we will search and evaluate only previously published aggregate data that already gained ethical approval.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HL and YFR conceptualized and designed the study. HL and YFR drafted the initial protocol. YTW and YY reviewed and revised the draft of this protocol. CZ revised the manuscript for important intellectual content. FMY coordinated and supervised all aspects of the work. All authors had discussed and approved the final version of the manuscript as submitted.

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Figures

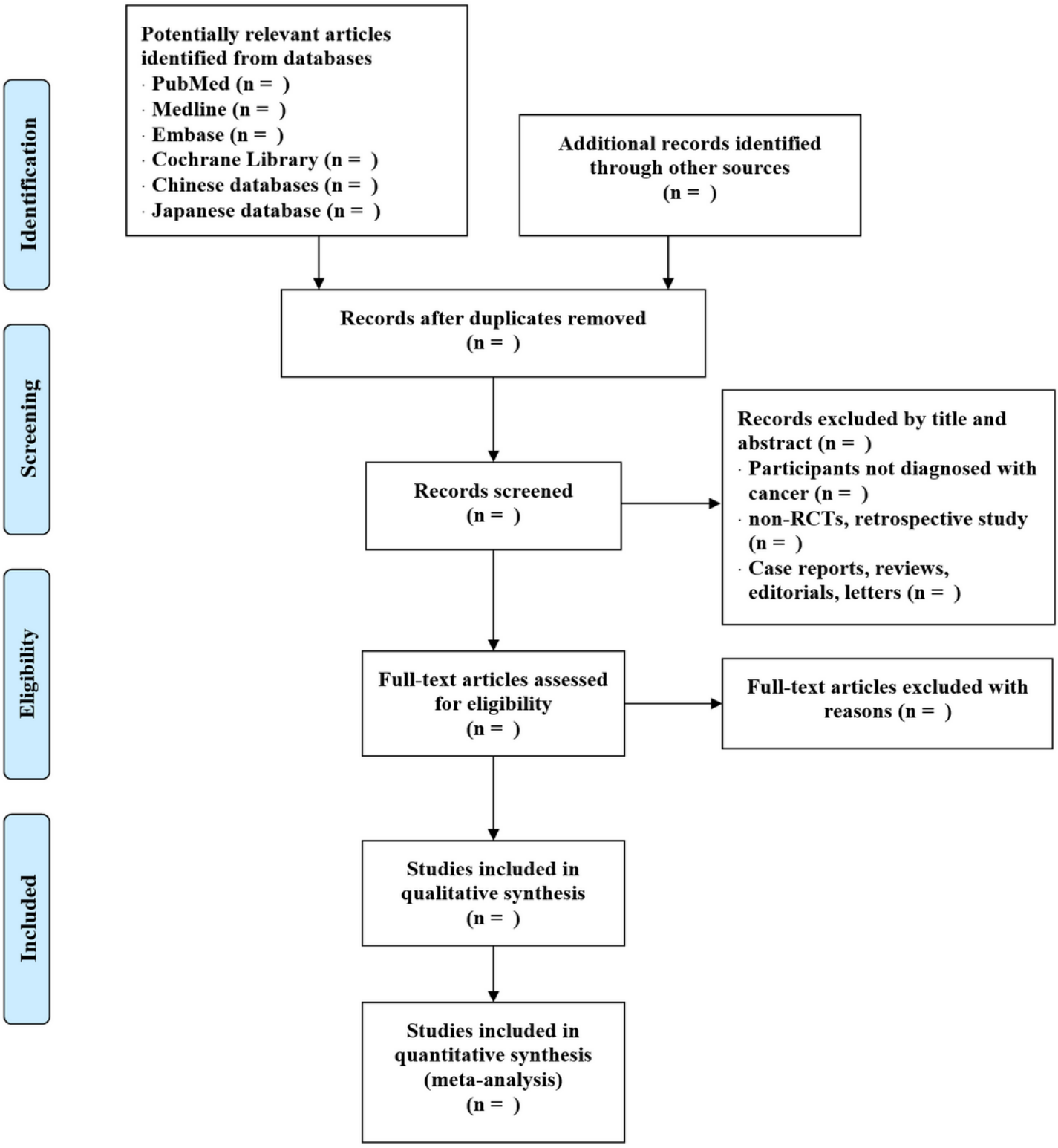

Figure 1

PRISMA flow diagram of the study selection process.

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