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Chinese herbal medicine as adjuvant treatment in patients receiving laparoscopic surgery: A protocol for systematic review and meta-analysis

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Keywords: Herbal medicine < THERAPEUTICS, COMPLEMENTARY MEDICINE, SURGERY, Gastroduodenal disease < GASTROENTEROLOGY, Systematic Review
Chinese herbal medicine as adjuvant treatment in patients receiving laparoscopic surgery: A protocol for systematic review and meta-analysis

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WORD COUNT: 2,713 words
ABSTRACT

Introduction: Postoperative nausea and vomiting (PONV) is a distressing symptom that patients often complain of even after less invasive surgery such as laparoscopic surgery (LS). If PONV is not well managed, patient recovery and postoperative quality of life are adversely affected. Although various drugs have been administered to prevent PONV, their effectiveness is limited, and their adverse effects are numerous. Although herbal medicine has been widely used to manage various gastrointestinal symptoms, including nausea and vomiting, scientific evidence of its effects remains lacking. This protocol is intended for a systematic review to analyze the efficacy and safety of Chinese herbal medicine for PONV after LS through a meta-analysis.

Methods and analysis: Randomized controlled trials, reported until June 2022, will be retrieved from electronic databases, such as Medline, EMBASE, and Cochrane Library. We will compare the effects of herbal medicine in patients presenting with PONV after LS with those of Western medicine, placebo, and no-treatment. If sufficient studies are identified, we will evaluate the combined effects of herbal and Western medicine. The incidence of nausea and vomiting will be considered the primary outcome. The secondary outcomes will comprise the intensity of complaints, quality of life, and incidence of adverse events. Two independent reviewers will collect data based on the Preferred Reporting Items for Systematic Review and Meta-Analyses statement, evaluate the quality of each study using the Cochrane risk-of-bias tool, and synthesize the results via a meta-analysis if possible.

Ethics and dissemination: Ethical approval is not required for this review. The outcomes of this study will be disseminated in peer-reviewed journals and posters.

PROSPERO registration number: CRD42022345749.
STRENGTHS AND LIMITATIONS OF THIS STUDY:

- This systematic review protocol will critically follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols to ensure transparency and fairness in the process.

- This review will be the first to explore the safety and efficacy of not only Chinese herbal medicine but also its co-administration with Western medicine for nausea and vomiting after laparoscopic surgery.

- The results of this study will facilitate the decision-making process of patients, clinicians, and policymakers by establishing comprehensive evidence for postoperative nausea and vomiting management with herbal medicines.

- The grading of recommendation assessment, development, and evaluation systems will be employed to assess the quality of evidence to interpret review results in the fields of clinical medicine.

- An insufficient number of well-designed randomized controlled trials may be a limitation of this study.
1. INTRODUCTION

Postoperative nausea and vomiting (PONV) is a frequent complication of anesthesia or surgery and significantly affects patient discomfort and morbidity [1]. Nausea and vomiting are observed in 20%–30% of patients receiving surgery [2], with an incidence of approximately 60% in those receiving gynecological laparoscopic surgery (LS) [3].

The laparoscopic approach for surgeries such as splenectomy, cholecystectomy, and esophageal surgery allows for minimal invasion, which results in a better quality of life, less pain, and faster recovery than open surgery [4]; however, 40%–77% of patients experience PONV following LS [3].

PONV can be attributed to various etiologies, including patient conditions (e.g., age, body mass index, and underlying diseases), types of surgery, anesthesia-related factors, and postoperative factors (e.g., pain intensity and use of opioid analgesics) [1]. PONV requires appropriate management as it can delay discharge from the hospital, prolong patient recovery, and increase medical costs. To reduce the risk of PONV, the use of anesthetics and analgesics that make patients prone to vomiting should be avoided. For these reasons, the administration of prophylactic antiemetics is recommended to accelerate the patient’s recovery process [5]. However, antiemetic drugs, such as metoclopramide, droperidol, and ondansetron, have been effective in alleviating vomiting in only 20% of patients; they may also cause adverse effects, such as headache, constipation, and dizziness, or contribute to drug interactions. Therefore, the risk must be minimized by selecting the appropriate drug and dose according to the patient's health status and risk level [5].

Herbal medicine has been used for a long time to treat gastrointestinal symptoms such as nausea and vomiting. Many studies have explored the effectiveness of ginger (Zingiber officinale) in the treatment of nausea [6]. In some studies, ginger was more effective than placebo in preventing PONV after gynecological surgery [7,8]. Furthermore,
two randomized controlled trials (RCTs) have demonstrated the therapeutic effect of ginger as an antiemetic agent after both laparoscopic cholecystectomy and nephrectomy [9,10]. In relevant reviews, ginger has been reported to safely improve the severity of PONV, thus reducing the need for antiemetics and substituting their use [11-13]. However, some studies identified no significant difference in reducing the incidence of PONV between ginger and placebo groups [14,15]. Considering the overall results of previous studies, the scientific evidence to recommend herbal medicine for the treatment of PONV after LS is still limited.

As studies to date on herbal medicine for PONV are limited to the use of ginger, more comprehensive research is required. Thus, in this review, we will search for studies of Chinese herbal medicine, including ginger and other herbs, to evaluate the safety and efficacy of complementary and alternative medicine in managing patients receiving surgery. This review will focus on LS, which can cause more nausea and vomiting by directly affecting the abdominal organs. We intended to explore the safety and effectiveness of herbal medicine and its co-administration with Western medicine, offering an alternative treatment option to counteract the side effects of antiemetics.

This review aims to investigate the effectiveness and safety of Chinese herbal medicine in patients with PONV after LS.

2. METHODS AND ANALYSIS

2.1. Study design and registration

This systematic review protocol was registered in the PROSPERO database (registration ID: CRD42022345749). The study will be performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) [16].

2.2. Eligibility criteria
We used Population, Intervention, Comparison, Outcome and Study design as a framework to develop the search strategy as well as the inclusion and exclusion criteria for our systematic review as follows: population (patients suffering from PONV after LS), intervention (Chinese herbal medicine), comparison (herbal medicine group vs. control group [no herbal medicine]), outcome (incidence of nausea and vomiting), and study design (RCTs).

2.2.1. Types of studies
This review will include RCTs, such as multi-arm trials involving eligible interventions. Meanwhile, animal experiments, case studies, study protocols, and commentary articles will be excluded.

2.2.2. Types of participants
We will review studies involving patients with complaints of nausea and vomiting after LS, with no restrictions on sex, age, or race. Patients with nausea or vomiting attributable to conditions other than LS, such as pregnancy, will be excluded.

2.2.3. Types of interventions
Studies on the use of herbal medicines for treating nausea and vomiting after LS will be included (any dose, dosing time, frequency, or duration). Only studies involving the oral route of administration will be considered for inclusion, and those that used aromatherapy and herbal decoction enemas will be excluded. All dosage forms of herbs, such as powders, granules, and extracts, will be considered experimental interventions. We will exclude studies using herbal decoctions or extract granules with no details on the composition and administration information available. We will include studies with Western medicine, placebo, and no-treatment as comparator groups.
2.2.4. Types of comparisons

We will include studies involving the following types of comparisons: herbal medicine versus comparators (Western medicine, placebo, and no-treatment). If sufficient studies are identified, we will compare the efficacy of combination therapy (herbal and Western medicine) for nausea and vomiting with that of conventional Western medicine alone.

2.2.5. Types of outcome measures

The primary outcomes will include the incidence of nausea and vomiting. The secondary outcomes will include the frequency and intensity of both nausea and vomiting; time to symptom improvement; frequency of rescue antiemetic requirements; and incidence of adverse events.

2.3. Data source and search strategy

2.3.1. Database resources

The following 11 electronic databases will be searched for articles published from inception until June 2022, without any language restrictions: the English databases, including Allied and Complementary Medicine Database, Cochrane Central Register of Controlled Trials, EMBASE, and Medline via PubMed; the Korean databases, including KoreaMed, Korean Medical Database, Korean Studies Information Service System, National Digital Science Library, and Oriental Medicine Advanced Searching Integrated System; the Chinese database China National Knowledge Infrastructure; and the Japanese database Citation Information by NII.

If possible, additional data from registries such as the Clinical Research Information Service and ClinicalTrials.gov will be searched. We will check the relevant grey literature, such as
ongoing research and committee reports, using Google Scholar and OpenGrey.

2.3.2. Search strategy

We will use the search terms “nausea and vomiting” and “herbal medicine,” which are indicative of the disease and intervention, respectively. The search strategy for Medline is presented in Table 1, and its modified versions will be applied according to the instructions of each database.

Table 1. Search strategy used in Medline via PubMed.

<table>
<thead>
<tr>
<th>No.</th>
<th>Search items</th>
</tr>
</thead>
<tbody>
<tr>
<td>#6</td>
<td>&quot;Nephrolithotomy, Percutaneous*[MH] OR &quot;Percutaneous Nephrolithotomy*[TW] OR &quot;PCNL*[TW] OR &quot;percutaneous kidney stone removal*[TW]</td>
</tr>
<tr>
<td>#7</td>
<td>#1 OR #2 OR #3 OR #4 OR #5 OR #6</td>
</tr>
<tr>
<td>#9</td>
<td>Nausea*[MH] OR Nausea*[TW] OR ((postpro*[TW] OR postsurg*[TW]) AND nausea) OR &quot;Nausea, Postoperative*[TW]</td>
</tr>
</tbody>
</table>
2.4. Data collection and assessment

2.4.1. Study selection

Two independent reviewers (N-YH and M-JP) will screen the titles and abstracts to determine the eligibility of articles for this review. Articles will be collected and sorted using EndNote 20 (Clarivate Analytics, London, UK). After screening, investigators will independently review the full-text articles to exclude irrelevant articles. Any disagreement between the two researchers throughout the review process will be arbitrated by a third party (JK). The details of this procedure are presented in the PRISMA flow diagram (Fig. 1) [17].

2.4.2. Data extraction

Two researchers will independently collect and manage the necessary research data through a predesigned standard data extraction form using Microsoft Excel (2019). The collected data will be confirmed by the third author. We will extract the following study information: basic information of the study, including the first author, publication year, country, and study design; characteristics of participants, including the mean age, sex distribution, and sample size; interventions, including name, formulation, and composition of prescription, control type, dosage, and administration period; and outcomes, including outcome measures, results,
and statistical difference.

In the case of missing data, we will contact the corresponding author of the article by e-mail to supplement the details.

2.4.3. Quality assessment

The methodological quality of the included studies will be assessed using a revised version of the Cochrane tool for assessing the risk of bias in randomized trials. Two independent reviewers will evaluate the risk of bias for each study. Disagreements among reviewers will be reconciled through discussion, assisted by an arbitrator if necessary. The five domains of bias are as follows: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in outcome measurement, and bias in selection of the reported result. The assessments of bias for each domain are “low risk of bias,” “some concerns,” or “high risk of bias” [18].

The Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach will be employed to assess the quality of evidence and interpret the results of this systematic review using the GRADEpro GDT software, which will be based on the categories of study limitations; inconsistency of results, indirectness of evidence, imprecision, and reporting bias [19].

2.5. Data analysis and synthesis

2.5.1. Analysis and synthesis procedure

Data will be pooled using the Review Manager software (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The outcomes will be presented as the risk ratio for discrete outcomes (e.g., incidence rate of nausea) and as the mean difference for continuous outcomes (e.g., intensity of nausea) with a 95% confidence
interval. Quantitative synthesis will be applied if methodological similarities are guaranteed between more than two RCT reports; otherwise, a narrative summary and tabulation will be presented.

2.5.2. Assessment of heterogeneity

Statistical heterogeneity among the articles will be quantified using $I^2$ statistics for the meta-analysis. The outcomes will be treated under a random-effects model with significant heterogeneity ($I^2 > 50\%$ may represent substantial heterogeneity); if not, a fixed-effects model will be applied.

2.5.3. Sensitivity analysis

Sensitivity analysis will be conducted to assess the robustness of the results by deleting studies with unclear findings and those with a high risk of bias in methodological quality.

2.5.4. Assessment of publication bias

A funnel plot will be used to assess publication bias if more than ten relevant studies are identified.

2.5.5. Analysis of subgroups

A subgroup analysis will be performed according to the types of surgery and Chinese herbal medicine. Variables such as dosage and formulation of herbal medicine and treatment period may also be considered in the sub-analyses if there are sufficient data.

3. ETHICS AND DISSEMINATION

Ethical approval is not required for this review because it is intended to analyze the results of
previous trials in which participants have already consented to the purpose of the study. The results of this study will be disseminated to peer-reviewed journals and posters.

4. PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not involved in the design process, data research, or preparation for this study.

5. DISCUSSION

PONV is a subjective discomfort experienced by approximately one-third of patients receiving surgery [1,20]. It can lead to dehydration, electrolyte imbalance, or even aspiration pneumonia [21]. Patients with PONV spend 30% more time in the post-anesthesia care unit postoperatively, extending from 3 to 4 h on average, compared to those without it. Additionally, the total cost of postoperative recovery was approximately 14% higher in patients with PONV than in those without PONV ($730 vs. $640). With the failure to manage symptoms of PONV, the treatment period is prolonged, thus increasing economic cost and adversely affecting patients’ quality of life [20]. Nevertheless, PONV management has been considered less important than pain.

LS is less invasive than open surgery and has the advantages of less bleeding and pain, fewer complications, and faster recovery, resulting in a better quality of life [4,22,23]. Thus, LS is preferred as a surgical practice; however, a high incidence of PONV after LS remains a cause of concern for both patients and surgeons [4]. A possible explanation for PONV is intestinal ischemia caused by increased intra-abdominal pressure, triggering the release of serotonin [24]. To prevent PONV, various antiemetic drugs, including metoclopramide, droperidol, and dexamethasone, have been administered; however, well-
defined management guidelines for PONV have not yet been formulated [1]. Additionally, headache and dizziness have been reported as common side effects of certain antiemetics [25]. Therefore, drug-related adverse effects and postoperative complications must be properly managed for the rapid recovery of patients receiving surgery [5].

To overcome the limitations of these treatment options, studies on the prevention of PONV have been conducted using complementary and alternative medicines, such as Chinese herbal medicine. In traditional medicine, ginger has been widely used to treat nausea and evaluated for its antiemetic efficacy on PONV for a long time [6]; however, the data are insufficient to clarify its effect [26]. According to a recent meta-analysis based on two RCTs with 212 participants after obstetrical/gynecological surgery [27], a single herb ginger significantly improved both nausea and vomiting compared to placebo. However, since combination prescriptions containing multiple herb species are prescribed more frequently than single herbs in clinical fields, it is necessary to synthesize various kinds of herbal preparations and analyze their overall effectiveness on PONV.

This systematic review aims to analyze the effects of Chinese herbal medicine compared to placebo or Western medicine for treating PONV caused by LS. This study will investigate whether the quality of life and complications of surgical patients can be managed and improved with concurrent administration of herbal and Western medicines compared with the discrete use of Western medicine. We will search multiple databases with a reproducible search plan, and include both published and unpublished papers to cover all possible outcome variables.

A potential limitation that may affect the final conclusions of this study is the poor methodological quality of the included studies. However, to the best of our knowledge, this review will be the first to comprehensively assess and synthesize clinical evidence of the preventive and therapeutic effects of Chinese herbal medicine and combination therapy on
nausea and vomiting after LS. These future findings will facilitate the decision making of patients, clinicians, and policymakers by establishing evidence for the management of PONV related to LS with herbal medicine and providing guidelines for its use. Therefore, we plan to submit the results of this systematic review for publication in a peer-reviewed journal and disseminate clinical data to anyone upon reasonable request.

Authors’ contributions
This study was first conceptualized by N-YH and M-JP. The protocol was designed by N-YH and JK. N-YH and M-JP conducted the data search and investigation in this study. The original draft of this manuscript was written by N-YH, and finally confirmed by JK. All authors read and approved the final version of this article.

Funding
This research was supported by a grant from the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI20C0865). The funders had no role in the study design, data collection, or manuscript preparation.

Competing interests
The authors have no conflicts of interest to disclose.

REFERENCES
1 Acalovschi I. Postoperative nausea and vomiting. Curr Anaesth Crit Care


**FIGURE LEGENDS**

**Figure 1.** Flowchart of the search process.
Records identified through database searching and other sources:
- Databases (n = )
- Registers (n = )

Records removed before screening:
- Duplicate (n = )
- Other reasons (n = )

Records screened (n = )

Records excluded (n = )

Reports sought for retrieval (n = )

Reports not retrieved (n = )

Reports assessed for eligibility (n = )

Reports excluded:
- Inappropriate populations (n = )
- Inappropriate interventions (n = )
- Not available (n = )

Studies included in the review (n = )
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

<table>
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<th>Item No</th>
<th>Checklist item</th>
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<td>1a</td>
<td>Identify the report as a protocol of a systematic review</td>
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<td>Registration</td>
<td>2</td>
<td>If registered, provide the name of the registry (such as PROSPERO) and registration number</td>
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</tr>
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<td>Authors:</td>
<td>3a</td>
<td>Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
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</tr>
<tr>
<td>Contributions</td>
<td>3b</td>
<td>Describe contributions of protocol authors and identify the guarantor of the review</td>
<td>14</td>
</tr>
<tr>
<td>Amendments</td>
<td>4</td>
<td>If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments</td>
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<td>Indicate sources of financial or other support for the review</td>
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<td>Sponsor</td>
<td>5b</td>
<td>Provide name for the review funder and/or sponsor</td>
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</tr>
<tr>
<td>Role of sponsor or funder</td>
<td>5c</td>
<td>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</td>
<td>14</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>6</td>
<td>Describe the rationale for the review in the context of what is already known</td>
<td>4,5</td>
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<tr>
<td>Objectives</td>
<td>7</td>
<td>Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)</td>
<td>5</td>
</tr>
<tr>
<td>METHODS</td>
<td>8</td>
<td>Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review</td>
<td>5,6</td>
</tr>
<tr>
<td>Information sources</td>
<td>9</td>
<td>Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage</td>
<td>7,8</td>
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<tr>
<td>Search strategy</td>
<td>10</td>
<td>Present draft of search strategy to be used for at least one electronic database, including planned limits such that it could be repeated</td>
<td>8,Table 1</td>
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<td>Study records:</td>
<td>11a</td>
<td>Describe the mechanism(s) that will be used to manage records and data throughout the review</td>
<td>9</td>
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<tr>
<td></td>
<td>11b</td>
<td>State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)</td>
<td>9, Figure 1</td>
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<tr>
<td></td>
<td>11c</td>
<td>Describe planned method of extracting data from reports (such as piloting forms, done independently and duplicate), any processes for obtaining and confirming data from investigators</td>
<td>9</td>
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<tr>
<td>Data collection process</td>
<td>11c</td>
<td>Describe planned method of extracting data from reports (such as piloting forms, done independently and duplicate), any processes for obtaining and confirming data from investigators</td>
<td>9</td>
</tr>
<tr>
<td>Data items</td>
<td>12</td>
<td>List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications</td>
<td>9,10</td>
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<tr>
<td>Outcomes and prioritization</td>
<td>13</td>
<td>List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale</td>
<td>7</td>
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<tr>
<td>Risk of bias in individual studies</td>
<td>14</td>
<td>Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis</td>
<td>10</td>
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<tr>
<td>Data synthesis</td>
<td>15a</td>
<td>Describe criteria under which study data will be quantitatively synthesised</td>
<td>11</td>
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<td></td>
<td>15b</td>
<td>If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ)</td>
<td>10,11</td>
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<td></td>
<td>15c</td>
<td>Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)</td>
<td>11</td>
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<td></td>
<td>15d</td>
<td>If quantitative synthesis is not appropriate, describe the type of summary planned</td>
<td>11</td>
</tr>
<tr>
<td>Meta-bias(es)</td>
<td>16</td>
<td>Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)</td>
<td>11</td>
</tr>
<tr>
<td>Confidence in cumulative evidence</td>
<td>17</td>
<td>Describe how the strength of the body of evidence will be assessed (such as GRADE)</td>
<td>10</td>
</tr>
</tbody>
</table>

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

Chinese herbal medicine as adjuvant treatment for postoperative nausea and vomiting in patients undergoing laparoscopic surgery: A protocol for systematic review and meta-analysis

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<td>Date Submitted by the Author:</td>
<td>26-May-2023</td>
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<tr>
<td>Complete List of Authors:</td>
<td>Ha, Na-Yeon; Kyung Hee University Medical Center, Department of Internal Korean Medicine, Division of Digestive Diseases Park, Mu-Jin; Kyung Hee University, Graduate School, Department of Clinical Korean Medicine Kim, Jinsung; Kyung Hee University Medical Center, Kyung Hee University College of Korean Medicine, Department of Gastroenterology</td>
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<td>Secondary Subject Heading:</td>
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Na-Yeon Ha,¹ Mu-Jin Park,² Jinsung Kim³

¹Division of Digestive Diseases, Department of Internal Korean Medicine, Kyung Hee University Medical Center, Seoul, Korea

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E-mail: oridoc@khu.ac.kr

WORD COUNT: 2,582 words
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PROSPERO registration number: CRD42022345749.
STRENGTHS AND LIMITATIONS OF THIS STUDY:

- This systematic review protocol will critically follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols to ensure transparency and fairness in the process.

- This review will explore the safety and efficacy of not only Chinese herbal medicine but also its co-administration with Western medicine for nausea and vomiting after laparoscopic surgery.

- Two independent reviewers will screen the titles, abstracts, and full-text articles obtained from various databases in this systematic review.

- Grading of recommendation assessment, development, and evaluation systems will be employed to assess the quality of evidence to interpret review results in the fields of clinical medicine.

- An insufficient number of well-designed randomized controlled trials may be a limitation of this study.
1. INTRODUCTION

Postoperative nausea and vomiting (PONV) is a frequent complication of anesthesia or surgery and significantly affects patient discomfort and morbidity [1]. Nausea and vomiting are observed in 20–30% of patients undergoing surgery [2], with an incidence of approximately 60% in those undergoing gynecological laparoscopic surgery (LS) [3].

The laparoscopic approach for surgeries, such as splenectomy, cholecystectomy, and esophageal surgery, allows for minimal invasion, which results in a better quality of life, less pain, and faster recovery than open surgery [4]; however, 40–77% of patients experience PONV following LS [3].

PONV can be attributed to various etiologies, including patient conditions (e.g., age, body mass index, and underlying diseases), type of surgery, anesthesia-related factors, and postoperative factors (e.g., pain intensity and use of opioid analgesics) [1]. PONV requires appropriate management as it can delay discharge from the hospital, prolong patient recovery, and increase medical costs. The use of anesthetics and analgesics that make patients prone to vomiting should be avoided to reduce the risk of PONV. For these reasons, the administration of prophylactic antiemetics is recommended to accelerate the patient’s recovery process [5]. However, antiemetic drugs, such as metoclopramide, droperidol, and ondansetron, have been effective in alleviating vomiting in only 20% of patients; they may also cause adverse effects, such as headache, constipation, and dizziness, or contribute to drug interactions. Therefore, the risk must be minimized by selecting the appropriate drug and dose according to the patient's health status and risk level [5].

Herbal medicine has long been used to treat gastrointestinal symptoms such as nausea and vomiting. Many studies have explored the effectiveness of ginger (*Zingiber officinale*) in the treatment of nausea [6,7]. In some studies, ginger was more effective than placebo in preventing PONV after gynecological surgery [8,9]. Furthermore, two randomized
controlled trials (RCTs) demonstrated the therapeutic effect of ginger as an antiemetic agent after laparoscopic cholecystectomy and nephrectomy [10,11]. In relevant reviews, ginger has been reported to safely improve the severity of PONV, thus reducing the need for antiemetics and substituting their use [12-14]. However, some studies identified no significant difference in reducing the incidence of PONV between the ginger and placebo groups [15,16]. Considering the overall results of previous studies, scientific evidence to recommend herbal medicine for the treatment of PONV after LS remains limited.

To date, as studies on herbal medicines for PONV are limited to the use of ginger, more comprehensive research is required. Thus, in this review, we will search for studies on Chinese herbal medicine, including ginger and other herbs, to evaluate the safety and efficacy of complementary and alternative medicine in managing patients undergoing surgery. This review will focus on LS, which can cause more nausea and vomiting through directly affecting the abdominal organs. We aimed to explore the safety and effectiveness of herbal medicine and its co-administration with Western medicine, offering an alternative treatment option to counteract the side effects of antiemetics.

This review aims to investigate the effectiveness and safety of Chinese herbal medicine in patients with PONV after LS.

2. METHODS AND ANALYSIS

2.1. Study design and registration

This systematic review protocol is registered in the PROSPERO database (registration ID: CRD42022345749). The study will be performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) [17]. We have not yet begun the final data extraction stage of the review.
2.2. Eligibility criteria

We used population, intervention, comparison, outcome, and study design as a framework to develop the search strategy as well as the inclusion and exclusion criteria for our systematic review as follows: population (patients experiencing PONV after LS), intervention (Chinese herbal medicine), comparison (herbal medicine vs. control group [no herbal medicine]), outcome (incidence of nausea and vomiting), and study design (RCTs).

2.2.1. Types of studies

This review will include RCTs, such as multi-arm trials, involving eligible interventions. Animal experiments, case studies, study protocols, and commentary articles will be excluded.

2.2.2. Types of participants

We will review studies involving patients with complaints of nausea and vomiting after LS, with no restrictions on sex, age, or race. Patients with nausea or vomiting attributable to conditions other than LS, such as pregnancy, will be excluded.

2.2.3. Types of interventions

Studies on the use of herbal medicines to prevent and treat nausea and vomiting after LS will be included (any dose, dosing time, frequency, or duration). Only studies involving the oral route of administration will be considered for inclusion, and those that used aromatherapy and herbal decoction enemas will be excluded. All dosage forms of herbs, such as powders, granules, and extracts, will be considered experimental interventions. We will exclude studies using herbal decoctions or extract granules with no details on the composition and administration information. We will include studies with Western medicine, placebo, and no treatment as comparator groups.
2.2.4. Types of comparisons

We will include studies involving the following types of comparisons: herbal medicine versus comparators (Western medicine, placebo, and no treatment). If sufficient studies are identified, we will compare the efficacy of combination therapy (herbal and Western medicine) for nausea and vomiting with that of conventional Western medicine.

2.2.5. Types of outcome measures

The primary outcome will include the cumulative incidence of patients with nausea and/or vomiting over time postoperatively (e.g., 3, 6, 12, and 24 h post-LS). The secondary outcomes will include the frequency and intensity of both nausea and vomiting, time to symptom improvement, frequency of rescue antiemetic requirements, and incidence of adverse events.

2.3. Data source and search strategy

2.3.1. Database resources

The following 11 electronic databases will be searched for articles published from inception until June 2022, without any language restrictions: the English databases, including the Allied and Complementary Medicine Database, Cochrane Central Register of Controlled Trials, EMBASE, and Medline via PubMed; the Korean databases, including KoreaMed, Korean Medical Database, Korean Studies Information Service System, National Digital Science Library, and Oriental Medicine Advanced Searching Integrated System; the Chinese database China National Knowledge Infrastructure; and the Japanese database Citation Information by NII.

If possible, additional data from registries, such as the Clinical Research Information Service
and ClinicalTrials.gov, will be searched. We will check the relevant gray literature, such as ongoing research and committee reports, using Google Scholar and OpenGrey.

2.3.2. Search strategy

We will use the search terms “nausea and vomiting” and “herbal medicine,” which are indicative of the disease and intervention, respectively. The search strategy for Medline is presented in Table 1, and its modified versions will be applied according to the instructions of each database.

Table 1. Search strategy used in Medline via PubMed.

<table>
<thead>
<tr>
<th>No.</th>
<th>Search items</th>
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<tbody>
<tr>
<td>#6</td>
<td>&quot;Nephrolithotomy, Percutaneous*[MH] OR &quot;Percutaneous Nephrolithotomy*[TW] OR &quot;PCNL*[TW] OR &quot;percutaneous kidney stone removal*[TW]</td>
</tr>
<tr>
<td>#7</td>
<td>#1 OR #2 OR #3 OR #4 OR #5 OR #6</td>
</tr>
</tbody>
</table>
2.4. Data collection and assessment

2.4.1. Study selection

Two independent reviewers (N-YH and M-JP) will screen the titles and abstracts to determine the eligibility of the articles for this review. Articles will be collected and sorted using EndNote 20 (Clarivate Analytics, London, UK). After screening, investigators will independently review the full-text articles to exclude irrelevant articles. Any disagreement between the two researchers throughout the review process will be arbitrated by a third party (JK). The details of this procedure are presented in the PRISMA flow diagram (Fig. 1) [18].

2.4.2. Data extraction

Two researchers will independently collect and manage the necessary research data through a predesigned standard data extraction form using Microsoft Excel (2019). The collected data will be verified by the third author, and the translation will be validated by an independent professional translator consultant. We will extract the following information: basic information of the study, including the first author, publication year, country, and study design; characteristics of participants, including the mean age, sex distribution, and sample
size; interventions, including name, formulation, and composition of prescription, control type, dosage, and administration period; and outcomes, including outcome measures, results, and statistical differences.

In the case of missing data, we will contact the corresponding author of the article by e-mail to supplement the details.

2.4.3. Quality assessment

The methodological quality of the included studies will be assessed using a revised version of the Cochrane tool to assess the risk of bias in randomized trials. Two independent reviewers will evaluate the risk of bias for each study. Disagreements among reviewers will be reconciled through discussion, assisted by an arbitrator, if necessary. The five domains of bias are as follows: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in outcome measurement, and bias in selection of the reported result. The assessments of bias for each domain are “low risk of bias,” “some concerns,” or “high risk of bias” [19].

The Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach will be employed to assess the quality of evidence and interpret the results of this systematic review using the GRADEpro GDT software, which will be based on the categories of study limitations: inconsistency of results, indirectness of evidence, imprecision, and reporting bias [20].

2.5. Data analysis and synthesis

2.5.1. Analysis and synthesis procedure

Data will be pooled using the Review Manager software (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The outcomes will be
presented as the risk ratio for discrete outcomes (e.g., incidence rate of nausea) and mean difference for continuous outcomes (e.g., intensity of nausea) with a 95% confidence interval. Quantitative synthesis will be applied if methodological similarities are guaranteed between more than two RCT reports; otherwise, a narrative summary and tabulation will be presented.

2.5.2. Assessment of heterogeneity

Statistical heterogeneity among the articles will be quantified using I² statistics for the meta-analysis. The outcomes will be treated under a random-effects model with significant heterogeneity (I² > 50% may represent substantial heterogeneity); otherwise, a fixed-effects model will be applied.

2.5.3. Sensitivity analysis

Sensitivity analysis will be conducted to assess the robustness of the results via deleting studies with a high overall bias in methodological quality (high: any trial evaluated as “high risk of bias” for more than three domains).

2.5.4. Assessment of publication bias

A funnel plot will be used to assess publication bias if more than 10 relevant studies are identified.

2.5.5. Analysis of subgroups

A subgroup analysis will be performed according to the type of surgery and Chinese herbal medicine. Variables, such as dosage and formulation of herbal medicine and treatment period, may also be considered in the sub-analyses if sufficient data are available.
3. ETHICS AND DISSEMINATION

Ethical approval is not required for this review because it is aimed to analyze the results of previous trials in which participants have already consented to the purpose of the study. The results of this study will be disseminated to peer-reviewed journals and posters.

4. PATIENT AND PUBLIC INVOLVEMENT

The patients and public were not involved in the design process, data research, or preparation for this study.

5. DISCUSSION

PONV is a subjective discomfort experienced by approximately one-third of patients undergoing surgery [1,21]. It can lead to dehydration, electrolyte imbalance, and aspiration pneumonia [22]. Patients with PONV spend 30% more time in the post-anesthesia care unit postoperatively, extending from 3 to 4 h on average, compared with those without it. Additionally, the total cost of postoperative recovery was approximately 14% higher in patients with than in those without PONV ($730 vs. $640, respectively). With the failure to manage the symptoms of PONV, the treatment period is prolonged, thus increasing the economic cost and adversely affecting patients’ quality of life [21]. Nevertheless, PONV management has been considered less important than pain management.

LS is less invasive than open surgery and has the advantages of lower blood loss and fewer complications [23,24]. Thus, LS is preferred as a surgical practice; however, the high incidence of PONV after LS remains a cause of concern for both patients and surgeons [4]. A possible explanation for PONV is intestinal ischemia caused by increased intra-abdominal
pressure, which triggers the release of serotonin [25]. Well-defined management guidelines for PONV using various antiemetic drugs should be established to prevent and treat PONV, and drug-related adverse effects and postoperative complications must be properly managed for the rapid recovery of patients undergoing surgery [5,26].

Studies on the prevention of PONV have been conducted using complementary and alternative medicines, such as Chinese herbal medicine, to overcome the limitations of these treatment options. A single botanical drug, ginger, significantly improved both nausea and vomiting compared with placebo according to a recent meta-analysis based on two RCTs with 212 participants after obstetrical/gynecological surgery [27]; however, the evidence is still insufficient to clarify its effect [28]. In addition, as combination prescriptions containing multiple herb species are prescribed more frequently than single herbs in clinical fields, synthesizing various herbal preparations and analyzing their overall effectiveness in PONV are necessary.

This systematic review aims to analyze the effects of Chinese herbal medicine compared with placebo or Western medicine for treating PONV caused by LS. This study will investigate whether the quality of life and complications of surgical patients can be managed and improved with concurrent administration of herbal and Western medicines compared with the discrete use of Western medicine. We will search multiple databases with a reproducible search plan, and include both published and unpublished papers to cover all possible outcome variables.

A potential limitation that may affect the final conclusions of this study is the poor methodological quality of the included studies. However, to the best of our knowledge, this review will be the first to comprehensively assess and synthesize clinical evidence of the preventive and therapeutic effects of Chinese herbal medicine and combination therapy on nausea and vomiting after LS. These future findings will facilitate the decision making of
patients, clinicians, and policymakers through establishing evidence for the management of PONV related to LS with herbal medicine and providing guidelines for its use. Therefore, we plan to submit the results of this systematic review for publication in a peer-reviewed journal and disseminate the clinical data upon reasonable request.

Authors’ contributions
This study was first conceptualized by N-YH and M-JP. The protocol was designed by N-YH and JK. N-YH and M-JP conducted the data search and investigation in this study. The original draft of this manuscript was written by N-YH, and finally confirmed by JK. All authors read and approved the final version of this article.

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Competing interests
The authors have no conflicts of interest to disclose.

REFERENCES

1 Acalovschi I. Postoperative nausea and vomiting. Curr Anaesth Crit Care


12 Tóth B, Lantos T, Hegyi P, et al. Ginger (Zingiber officinale): An alternative for the


**FIGURE LEGENDS**

**Figure 1.** Flowchart of the search process.
Records identified through database searching and other sources:
  Databases \( (n = ) \)
  Registers \( (n = ) \)

Records removed before screening:
  Duplicate \( (n = ) \)
  Other reasons \( (n = ) \)

Records screened \( (n = ) \)

Records excluded \( (n = ) \)

Reports sought for retrieval \( (n = ) \)

Reports not retrieved \( (n = ) \)

Reports assessed for eligibility \( (n = ) \)

Reports excluded:
  Inappropriate populations \( (n = ) \)
  Inappropriate interventions \( (n = ) \)
  Not available \( (n = ) \)

Studies included in the review \( (n = ) \)
### PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

<table>
<thead>
<tr>
<th>Section and topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on Page #</th>
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<tbody>
<tr>
<td><strong>ADMINISTRATIVE INFORMATION</strong></td>
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<tr>
<td>Title:</td>
<td>1a</td>
<td>Identify the report as a protocol of a systematic review</td>
<td>1</td>
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<tr>
<td>Update</td>
<td>1b</td>
<td>If the protocol is for an update of a previous systematic review, identify as such</td>
<td>N/A</td>
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<tr>
<td>Registration</td>
<td>2</td>
<td>If registered, provide the name of the registry (such as PROSPERO) and registration number</td>
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<td>Authors:</td>
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<tr>
<td>Contact</td>
<td>3a</td>
<td>Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
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<tr>
<td>Contributions</td>
<td>3b</td>
<td>Describe contributions of protocol authors and identify the guarantor of the review</td>
<td>14</td>
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<tr>
<td>Amendments</td>
<td>4</td>
<td>If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments</td>
<td>N/A</td>
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<tr>
<td>Sources</td>
<td>5a</td>
<td>Indicate sources of financial or other support for the review</td>
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<td>Sponsor</td>
<td>5b</td>
<td>Provide name for the review funder and/or sponsor</td>
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<tr>
<td>Role of sponsor or funder</td>
<td>5c</td>
<td>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</td>
<td>14</td>
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<tr>
<td><strong>INTRODUCTION</strong></td>
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<tr>
<td>Rationale</td>
<td>6</td>
<td>Describe the rationale for the review in the context of what is already known</td>
<td>4,5</td>
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<tr>
<td>Objectives</td>
<td>7</td>
<td>Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)</td>
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<tr>
<td><strong>METHODS</strong></td>
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<tr>
<td>Eligibility criteria</td>
<td>8</td>
<td>Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review</td>
<td>6,7</td>
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<tr>
<td>Information sources</td>
<td>9</td>
<td>Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage</td>
<td>7,8</td>
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<tr>
<td>Search strategy</td>
<td>10</td>
<td>Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated</td>
<td>8,Table 1</td>
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<td>Study records:</td>
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<tr>
<td>Data management</td>
<td>11a Describe the mechanism(s) that will be used to manage records and data throughout the review 9</td>
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<tr>
<td>Selection process</td>
<td>11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) 9, Figure 1</td>
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<tr>
<td>Data collection process</td>
<td>11c Describe planned method of extracting data from reports (such as piloting forms, done independently and duplicate), any processes for obtaining and confirming data from investigators 9, 10</td>
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<tr>
<td>Data items</td>
<td>11d List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications 9, 10</td>
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<tr>
<td>Outcomes and prioritization</td>
<td>12 List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale 7</td>
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<td>Risk of bias in individual studies</td>
<td>13 Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis 10</td>
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<tr>
<td>Data synthesis</td>
<td>14 Describe criteria under which study data will be quantitatively synthesised 10, 11</td>
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<tr>
<td>15a If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ) 11</td>
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<td>15b If quantitative synthesis is not appropriate, describe the type of summary planned 11</td>
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<td>15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) 11</td>
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<tr>
<td>15d If quantitative synthesis is not appropriate, describe the type of summary planned 11</td>
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<tr>
<td>Meta-bias(es)</td>
<td>16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) 11</td>
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<tr>
<td>Confidence in cumulative evidence</td>
<td>17 Describe how the strength of the body of evidence will be assessed (such as GRADE) 10</td>
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</table>

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.