


BMJ Open Systematic review of the effectiveness of complementary and alternative medicine on nausea and vomiting in children with cancer: a study protocol

Ka Yan Ho,¹ Katherine Ka Wai Lam,¹ Joyce Oi Kwan Chung,¹ Wei Xia,² Ankie Tan Cheung,² Long Kwan Ho,² Sau Ying Chiu,³ Godfrey Chi Fung Chan,⁴ Ho Cheung William Li 

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¹School of Nursing, The Hong Kong Polytechnic University, Hong Kong, China

²School of Nursing, The University of Hong Kong, Hong Kong, China

³Department of Paediatrics & Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong, China

⁴Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, China

Correspondence to

Dr Ho Cheung William Li; william3@hku.hk

ABSTRACT

Introduction Nausea and vomiting are two most common symptoms reported by children with cancer when they undergo active treatment. However, pharmacological treatment is not sufficient to manage these two symptoms, with over 40% of children still experience nausea and vomiting after receiving antiemetics. There has been an exponential growth of studies to demonstrate the effectiveness of different complementary complementary medicine (CAM) to control nausea and vomiting during cancer treatment. Appropriate application of CAM enhances the effectiveness of antiemetics, thus reducing the symptom burden on children as well as improving their general condition and quality of life during cancer treatment. Nevertheless, it remains unclear which CAM is the best approach to help children to prevent or reduce nausea and vomiting during and after cancer treatment. This paper describes a protocol for identifying, analysing and synthesising research evidence on the effectiveness of CAM on nausea and vomiting in children with cancer.

Methods and analysis A total of 10 databases will be searched to identify appropriate literature: MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, CINAHL, PsycINFO, LILACS, OpenSIGLE, the Chinese Biomedical Literature Database, the Chinese Medical Current Contents and the Chinese National Knowledge Infrastructure. All randomised controlled trials which meet the inclusion criteria will be included. The primary outcome is the changes in nausea and vomiting either assessed by self-reported and/or objective measures. Review Manager 5.3 will be used to synthesise the data, calculate the treatment effects, perform any subgroup analysis and assess the risk of bias.

Ethical and dissemination The results will be presented at international conferences and published in peer-reviewed journals. As no individual data will be involved in this review, ethical approval is not required.

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INTRODUCTION

Description of the condition

Cancer is a leading cause of death in children, with an annual incidence of 300 000 new cases worldwide.¹ Because of breakthroughs

Strengths and limitations of this study

- This review will employ a systematic approach to evaluate the effectiveness of complementary and alternative therapies in reducing nausea and vomiting among children with cancer.
- Screening and selection of studies and data extraction and management will be performed by two independent researchers.
- Meta-analysis may not be performed due to insufficient homogeneous studies.
- There may be deficient in high-quality trials to generate convincing conclusions.
- Clinical characteristics will confound the results if a subgroup analysis cannot be performed.

in medical treatment, the survival rate for most types of childhood cancer has now increased to >80%.² Despite the improved survival, children with cancer still experience substantial adverse effects of cancer treatment.²⁻⁴ The two most commonly reported symptoms are nausea and vomiting.³ Nausea is a subjective experience characterised by a feeling of impending vomiting,⁵ whereas vomiting is defined as retching and expulsion of the stomach's contents through the mouth accompanied by shivering and salivation.⁵ A previous study indicated that these two symptoms affected up to 70% of children undergoing chemotherapy.⁶ This prevalence is similar to that in adult patients with cancer, ranging from 60% to 72%.^{7,8}

The aetiology of nausea and vomiting in children with cancer is multifactorial,⁹ but it is generally believed to be largely related to chemotherapy, which is the most common type of treatment for childhood cancer.⁵ Chemotherapeutic agents circulating in the blood stimulate the chemoreceptor trigger zone and result in acute nausea and

vomiting.¹⁰ Likewise, repeated cycles of chemotherapy induce anticipatory nausea and vomiting, which is a learnt response to the treatment due to classical conditioning.¹¹ Another cause of nausea and vomiting is haematopoietic stem cell transplantation, which is a common treatment for children who have malignancy with bone marrow failure.¹² This can be explained by the gastroparesis that results from the administration of high-dose chemotherapy before stem cell transplantation.¹³ Radiotherapy can also lead to nausea and vomiting, but it depends on the treatment sites.¹⁴ Children who undergo radiotherapy in the upper abdominal region are at increased risk of nausea and vomiting because of the inflammatory substances released from the damaged gastrointestinal tissues.¹⁵ Those exposed to whole-brain radiation are similarly at risk because of increased intracranial pressure due to tissue swelling.¹⁶ Other causes of nausea and vomiting include anaesthesia given for surgery,¹⁷ analgesics (particularly opioids)¹⁸ and anxiety and emotional responses.⁵

Nausea and vomiting cause serious disruptions in patients' daily function and quality of life during cancer treatment.³⁻⁵ These two symptoms can also contribute to additional clinical problems, such as weight loss and cachexia.¹⁹ Such clinical problems have adverse effects on patients' general condition, interfering with their ability to continuously receive chemotherapy²⁰; this, in turn, lowers the dose that can be administered²¹ and can even delay the overall cancer treatment.²² Given such devastating impacts, interventions that can alleviate nausea and vomiting are crucial, particularly for children with cancer.^{23 24} The most effective antiemetics are currently 5-HT₃ inhibitors, followed by NK₁ inhibitors and neuroleptic drugs.²⁵ Nevertheless, pharmacological intervention alone is insufficient to manage nausea and vomiting, with >40% of children still experiencing nausea and vomiting after receiving antiemetics.²⁶

Description of the interventions

Limitations of pharmacological treatment have led to an increase in the use of complementary and complementary medicine (CAM) to manage nausea and vomiting.²⁷ According to the National Institutes of Health,²⁸ CAM refers to medical products and practices that are not regarded as part of standard medical care. The types of CAM most commonly used to control nausea and vomiting among children with cancer include acupressure,^{26 29 30} acupuncture,³¹ hypnotherapy,^{32 33} aromatherapy^{34 35} and creative arts therapy.³⁶

How the interventions might work

Acupressure

Acupressure originated from traditional Chinese medicine and is used to regulate the basal energy inside the body through stimulation of acupoints via pressure.^[37] The P6 acupoint is located on the ventral surface of the wrist and is considered to have antiemetic action.³⁷

Acupuncture

Acupuncture also stems from traditional Chinese medicine and shares the same principle as acupressure. However, instead of applying pressure, acupuncture stimulates acupoints by insertion of fine needles into the body.²⁹

Hypnotherapy

Hypnotherapy is a therapeutic technique used to produce changes in people's perception and cognition.³⁸ Hypnotherapy encompasses different methods, among which relaxation and imagination are the most commonly used in children with cancer.^{32 33} Through these methods, hypnotherapy helps people to achieve a deep state of psychological relaxation.³⁹ When under a state of deep relaxation, people can much more easily override automatic thoughts;⁴⁰ these include anticipatory nausea and vomiting, which are learned responses to cancer treatment.¹¹ Likewise, hypnosis can decrease sympathetic tone, which helps minimize the symptoms associated with sympathetic arousal, such as nausea and vomiting.⁴¹

Aromatherapy

Aromatherapy refers to the use of essential oils, which are volatile liquids extracted from plants using streams and/or pressure.⁴² Inhalation of these volatile molecules stimulates olfactory receptors to produce nerve impulses, which are transmitted along the olfactory nerve to reach the amygdala and limbic system,⁴³ interacting with the neuropsychological pathway to reduce nausea and vomiting.⁴⁴

Creative arts therapy

Creative arts therapy is a broad term encompassing different treatment modalities such as dance, music, art and drama.³⁶ It aims to facilitate people's emotional expression and improve their coping skills,^{36 45} thus minimising the perceived severity of nausea and vomiting during cancer treatment.

Why this review is important

In 2017, the Multinational Association of Supportive Care in Cancer reiterated the importance of managing nausea and vomiting among children with cancer. They also issued a guideline to provide a consensus for healthcare professionals on how these two symptoms can be managed using a pharmacological approach.⁶ However, these two symptoms remain a significant clinical concern for children with cancer.⁵ This concern might be due to healthcare professionals' perception that nausea and vomiting are solely biological problems as well as the heavy reliance of these professionals on pharmacological treatment for symptom management.⁴⁶ This point is particularly true because anticipatory nausea and vomiting are learnt responses to cancer and are difficult to control by medications alone.⁴⁷ Increasingly more studies are demonstrating the effectiveness of different types of CAM to control nausea and vomiting during cancer treatment.²⁷ Appropriate application of CAM enhances the

effectiveness of antiemetics, thus reducing the symptom burden on children as well as improving their general condition and quality of life during cancer treatment.

Objective

The objective of this review is to identify, analyse and synthesise research evidence of the effectiveness of CAM on treatment-related nausea and vomiting in children with cancer.

METHODS AND ANALYSIS

The systematic review will start in August 2019, and the planned end date is December 2020.

Patient and public involvement

No patient involved.

Criteria for considering studies for this review

Types of studies

To be included in this review, the article must be a fully published randomised trial. The trial can either adopt a parallel control design or a crossover design.

Types of participants

We will include all studies of patients aged ≤ 18 years who were diagnosed with any type of cancer and were undergoing active treatment for any type of cancer. However, we will exclude studies that involved patients receiving palliative treatment. Among studies of patients with diagnoses other than cancer, only those in which $\geq 50\%$ of the patients had diagnoses of cancer will be included in this review.

Types of interventions

Any type of CAM will be included in this review. However, interventions involving dietary supplements (eg, ginger powder or vitamins) to reduce nausea and vomiting will be excluded.

Types of outcome measures

Primary outcomes

- ▶ Nausea, assessed by self-reported and objective measures.
- ▶ Vomiting, assessed by self-reported and objective measures.

Secondary outcomes

- ▶ Compliance and adherence to the intervention.
- ▶ Any adverse event is defined as an unfavourable and unintended sign or symptom that occurs during the use of CAM but is not necessarily caused by it.⁴⁸ The most commonly reported adverse events of CAM include but are not limited to worsening symptoms, irritability, soreness, headache, pain, restlessness, sleep disturbance, infection, and tissue damage.^{49 50} To qualify as a reported adverse event, an incident must be explicitly referred to as an adverse event in the study. Health-related dropouts during the intervention period will also be counted as adverse events.⁵¹

Search method for study identification

The search will be conducted from 1 August 2019 to 30 September 2019. We will search the following 10 databases to identify relevant trials for this systematic review: MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE, CINAHL, PsycINFO, LILACS, OpenSIGLE, the Chinese Biomedical Literature Database, the Chinese Medical Current Contents and the Chinese National Knowledge Infrastructure. An expanded search will also be conducted to identify additional trials for review; for this expanded search, we will review the reference list of each selected article. The following four websites will also be searched: WHO International Clinical Trials Registry Platform (www.who.int/ictrp/en), Current Controlled Trials (www.controlled-trials.com), CenterWatch (www.centerwatch.com) and ClinicalTrials.gov (www.clinicaltrials.gov). A full electronic search strategy for one database, that is, Medline has been shown in the supplementary file.

Data collection and analysis

Selection of studies

The eligibility of each study will be independently assessed by two authors (KYH and WHCL) using a standardised form. A third author (GCFC), who is a senior researcher, will be consulted if the disagreement cannot be resolved by discussion. When multiple publications that belong to the same study are found, all of these publications will be marked with the same study identifier and all available data will be used.

Data extraction and management

To comply with the standards outlined in the Methodological Expectations of Cochrane Intervention Reviews,⁵² two authors will independently perform the data extraction using the data collection form for randomised controlled trials developed by Cochrane.⁵³ For each selected trial, the following information will be extracted:

1. Characteristics of the studies
 - Sponsorship and authors' affiliations.
 - Study design.
 - Method of generating random sequences.
 - Method of allocation concealment.
 - Degree of masking.
 - Any exclusion after randomisation.
 - Loss to follow-up.
 - Compliance.
 - Selective outcome reporting.
2. Characteristics of the study population
 - Country in which the trial was conducted.
 - Inclusion and exclusion criteria for each trial.
 - Number of subjects in each arm.
 - Demographic characteristics, including sex, age, educational attainment, ethnicity, socioeconomic status and religious beliefs.
 - Clinical characteristics, including type of cancer, cancer stage, age at diagnosis, time since diagnosis,

primary or secondary cancer, treatment modality and comorbidities.

3. Details of the intervention
 - Types of interventions.
 - Frequency, duration, total number of sessions and format (ie, on an individual or group basis).
 - Details of the control group.
 - Adherence.
 - Contamination.
4. Characteristics of outcomes
 - Self-reported measures.
 - Objective data.
 - Length of time between end of the intervention and outcome measurement.
 - Adverse events reported.

Any disagreement or ambiguity will be resolved through discussion with a third author (GCFC), who is a senior researcher in cancer care and symptom management. We will also contact the authors of each trial that was published within the last 10 years to seek clarification and obtain additional information or missing data. Similar data for each outcome will be extracted, if possible. If the trial contains multiple time points for primary outcomes, the outcome measured at the longest time interval will be selected for analysis. There is a well-established classification for chemotherapy-induced nausea and vomiting.¹³ Therefore, in the subgroup analysis of the effect of CAM on chemotherapy-induced nausea and vomiting, we will analyse the data according to three time points: anticipatory (within 24 hours prior to chemotherapy administration), acute (occurring within 24 hours of chemotherapy administration) and delayed (occurring 24 hours to 7 days after chemotherapy administration).^{13 54} Only adverse events that occurred during the intervention period will be included in the analysis. Adverse events that occurred during the follow-up (non-intervention) period will be excluded.⁵¹ All data will be entered and combined using Review Manager 5.3 (Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). The data entry process will involve two researchers: one (ATC) will enter the data into the software, and another (KKWL) will verify the entered data.

Assessment of risk of bias in included studies

The risk-of-bias assessment will follow the guideline in the *Cochrane Handbook for Systematic Reviews of Intervention*⁵⁵ and that in the *Cochrane Consumers and Communication Review Group*.⁵⁶ For randomised controlled trials, the following domains will be assessed:

- ▶ Sequence generation.
- ▶ Allocation concealment.
- ▶ Blinding of participants and personnel.
- ▶ Blinding of outcome.
- ▶ Selective outcome reporting.
- ▶ Incomplete outcome data.
- ▶ Other sources of bias.

For the randomised trials that adopted a crossover design, the assessment will be extended to cover

additional domains such as receiving the intervention in random order and evaluation of the carryover effect.^{55 56}

Two authors (KYH and WHCL) will independently assess the risk of bias of the included studies. They will evaluate the degree of risk (ie, low, high or unclear) according to the criteria established by Higgins and Green.⁵⁵ Comments from a third author (GCFC, a senior researcher) will be sought when disagreement occurs. The risk of bias of all included trials will be presented in a figure.

Measure of treatment effect

Review Manager 5.3 will be used to conduct a meta-analysis. We will measure the treatment effects using ORs for dichotomous outcomes and the mean difference (MD) and standardised mean difference (SMD) for continuous outcomes. The 95% CIs will be reported for all outcomes.

Units of analysis

Cluster randomization

The guideline stipulated in the *Cochrane Handbook of Systematic Reviews of Interventions* will be followed to manage the data from cluster randomised controlled trials.⁵⁵

First, we will check whether adequate adjustments have been made to account for clustering before estimating the treatment effects. If adequate adjustments have not been made, we will extract the data and estimate the treatment effect using a parallel control design, but we will adjust the standard errors to overcome the clustering effect. However, this analysis requires information on an appropriate intraclass correlation coefficient (ICC). Hence, we will contact the authors. If we fail to receive a response from the authors, we will estimate the ICC from the existing database or from the studies included in this review. If we are still unable to calculate an appropriate ICC, a sensitivity analysis will be conducted using a high ICC of 0.10, a moderate ICC of 0.01 and a low ICC of 0.00. We will use Review Manager 5.3 to combine the estimates obtained from clustered randomised controlled trials with those from studies with a parallel control design.

Crossover design

If a trial has adopted a crossover design, we will only use the data collected before the first crossover time point to avoid any possible carryover effect. If the trial did not report these data, we will contact the corresponding author. If we do not receive a response from the author, this trial will be excluded from our meta-analysis and its findings will only be reported narratively.

Missing data

We will handle missing data in accordance with the guideline stipulated in the *Cochrane Handbook for Systematic Reviews of Intervention*.⁵⁵ In particular, the following methods will be used:

- ▶ Contact the corresponding author to request missing data.
- ▶ Perform analysis of available cases.
- ▶ Address the potential impact of missing data on the findings of the review in the Discussion section.

Assessment of heterogeneity

For clinical heterogeneity, we will examine the distribution of the following factors:

- ▶ Age.
- ▶ Sex.
- ▶ Diagnosis.
- ▶ Treatment modality.

Any uneven distribution that is unexpected will be addressed in the review in detail. With respect to statistical heterogeneity, we will compute the I^2 statistic, which is an index to quantify the percentage of variance in a meta-analysis that is attributable to study heterogeneity rather than sampling error.^{57 58} The χ^2 test will also be conducted to examine the genuineness of that heterogeneity.

Assessment of reporting biases

We will strictly follow the search procedure described in this protocol (see Search method for study identification) to minimise any reporting bias. If we identify a sufficient number of studies (ie, ≥ 10), we will graphically examine the publication bias using funnel plots. According to the guideline stipulated in the *Cochrane Handbook for Systematic Reviews of Interventions*, we will apply the test proposed by Egger *et al*⁵⁹ to assess the funnel plot symmetry.

Data synthesis

The Cochrane Collaboration's statistical software (Review Manager 5.3) will be used for data synthesis. The data will be pooled for the meta-analysis when the included studies are sufficiently homogeneous with respect to subjects, interventions and outcomes. All similar studies will be pooled for a random-effects model to obtain the pooled intervention effect. The pooled intervention effect will be expressed in terms of the MD and 95% of CI if the outcome was reported as a continuous variable. If different scales were used to assess the outcome, the SMD will be used. If the outcome was measured as a dichotomous variable, we will convert the OR into the SMD as long as the underlying continuous measure followed an approximately normal distribution.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses will be performed for the primary outcomes if sufficient trials are available:

- ▶ Diagnosis.
- ▶ Stage of cancer.

If possible, we will also conduct a subgroup analysis to determine the effectiveness of CAM on nausea and vomiting caused by different cancer treatments (ie, chemotherapy and radiation). Because there is a clear classification for chemotherapy-induced nausea and vomiting,^{13 54} the primary outcomes for this subgroup analysis will be defined by the following time points:

- ▶ Anticipatory (within 24 hours prior to chemotherapy administration).

- ▶ Acute (occurring within 24 hours of chemotherapy administration).
- ▶ Delayed (occurring 24 hours to 7 days after chemotherapy administration).

Sensitivity analysis

If possible, a sensitivity analysis will be carried out to examine the impact of including low-quality studies in the meta-analysis. Studies with a high or unclear risk of bias will be excluded to check the robustness of the conclusions.

Ethics and dissemination

The results will be presented at international conferences and published in peer-reviewed journals. As no individual data will be involved in this review, ethical approval is not required.

DISCUSSION

During the past few decades, different complementary and alternative therapies have been applied to manage nausea and vomiting associated with active treatment among children with cancer.^{26 29-36} Nevertheless, no systematic review has yet been performed to compare the effectiveness of these therapies. We will fill this knowledge gap in the existing literature by conducting a systematic review on current evidence. The results are expected to assist health-care professionals in their clinical decision making, particularly in relation to which complementary and alternative therapies are the most effective for management of nausea and vomiting during cancer treatment.

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ORCID ID

Ho Cheung William LI <http://orcid.org/0000-0002-3195-7695>

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