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Development and Validation of an Evidence-based Auricular Acupressure Intervention for Managing Chemotherapy-induced Nausea and Vomiting in Breast Cancer Patients

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Abstract

Background: Auricular therapy (AT) has been utilized as a promising complementary health approach to alleviating chemotherapy-induced nausea and vomiting (CINV) in breast cancer patients. However, current evidence on AT for CINV management has been inconclusive, and relevant AT treatment protocols have varied considerably in the intervention dosages and acupoint formulas without an evidence-informed intervention protocol tailored to CINV symptoms. This study aimed to develop an evidence-based AT intervention protocol for CINV management in breast cancer patient receiving chemotherapy.

Methods: This study adopted the *Medical Research Council Framework for Developing and Evaluating Complex Interventions* to guide the AT intervention development process. The process consists of four steps: identification of the evidence base, identification of theories and practice standards, identification of cancer symptom characteristics, and modelling and validation. The preliminary AT intervention was then evaluated through a content validity study to identify its theoretical and practical appropriateness. The content validity index (CVI) was used to determine the consensus level of the panel.

Results: A preliminary AT intervention protocol, including a true AT intervention and a sham AT intervention, was developed based on research evidence identified from five systematic reviews, the homuncular reflex theory, the *zang-fu* organs and meridian theory, relevant AT practice standards, and the natural symptom progress of CINV. The true AT was designed as a daily manual acupressure for five consecutive days. While the sham AT was designed with the same intervention duration and acupoint formula as the true AT without manual acupressure. The content validity study demonstrated excellent consensus among the expert panel to support the AT intervention as a theoretically and practically feasible program with the item-level CVI ranging from 0.83 to 1.0 and the scale-level CVI reaching 1.0.

Conclusion: This study followed the MRC framework to develop an evidence-based AT intervention for CINV management which is well supported by systematic review research evidence, AT theories and practice standards, CINV symptom characteristics, and expert panel consensus. The AT intervention would be further evaluated in a pilot randomised controlled trial to confirm its utility, feasibility and acceptability in clinical settings.

Key words

Auricular Therapy; Nausea and Vomiting; Chemotherapy, Adjuvant; Neoplasms; Content Validity

1 Background

Chemotherapy-induced nausea and vomiting (CINV) has been universally regarded as one of the most prominent symptoms in breast cancer patients receiving chemotherapy [1]. CINV often occurs within the first day (24 hours) after chemotherapy (acute CINV) and can last several days afterwards (delayed CINV) [2]. Antiemetics such as 5-HT3 and NK1 receptor antagonists have been recommended for CINV management [3, 4]. However, a complete symptom alleviation with current pharmaceutical agents alone has been problematic as many cancer patients with antiemetics during chemotherapy can still experience various degrees of acute vomiting and nausea, while delayed symptoms are more commonly reported than acute ones [1, 5, 6]. The use of non-pharmacological methods adjuvant to antiemetics has therefore been utilized to achieve a comprehensive CINV management. A few approaches, such as acupressure, acupuncture, eletro-acupuncture, guided imagery, and massage, have been adopted for CINV alleviation with inconclusive research evidence [7-9]. Acupressure at P6 (Neiguan) acupoint has been widely applied as a convenient complementary health approach to controlling nausea and vomiting, however, research evidence on its effects for CINV management have remained uncertain and inconclusive given that contradictory study findings were identified in a few clinical trials [7-9]. Practical concerns regarding the feasibility and acceptability of some non-pharmacological interventions also warrant attention given their potentially serious adverse events and requirements for intensive training and supervised practice, which can pose significant burden to both practitioners and patients and limit the possibility of self-practice for ongoing symptom management. Roles of other convenient and risk-free non-pharmacological options for CINV management are worthy of further exploration.

Auricular therapy (AT) has been a popular complementary health approach to managing a variety of health problems [10, 11]. Potential mechanisms of AT have been well supported by the homuncular reflex theory and *zang-fu* organs and meridian theory which recognise a biological connection between auricular acupoints and pathological conditions occurred in other body regions [10, 11]. AT has been frequently adopted in clinical settings for the prophylaxis and treatment of CINV. One of our previous systematic reviews confirmed a promising role of AT for CINV alleviation [12]. However, the level of evidence has been rated as low given various degrees of methodological flaws and suboptimal outcome measures were identified in the analyzed trials [12]. In addition, this review indicated that the AT protocols utilized in current CINV trials varied considerably in terms of acupoint formula and intervention dosage [12] without an evidence-based and research-informed protocol. This study was therefore conducted to develop and validate an evidence-based AT intervention protocol for CINV management. This paper presents phase I study results and findings of a large clinical research project that contains multiple phases of studies to develop and evaluate an evidence-based AT protocol for alleviating CINV in breast cancer patients undergoing chemotherapy [13].

2 Methods

2.1 Overview of the research design

The research design follows the *Medical Research Council Framework for Developing and Evaluating Complex Interventions* (the "MRC framework") [14]. The MRC framework recommends a three-step process of "development-evaluation-implementation" and consists of four phases of design: **(1)** intervention protocol development; **(2)** intervention feasibility assessment and pilot testing; **(3)** evaluation of effectiveness and cost-effectiveness; **(4)** implementation and dissemination [14]. This study adopted phase I of the MRC framework to guide the development and validation process of the evidence-based AT intervention as an independent research project, which include: **a)** identification of the evidence base; **b)** identification of AT theories and practice standards; **c)** identification of CINV symptom characteristics; **d)** validation of the AT protocol. This study was approved by the Human Subjects Ethics Sub-Committee at The Hong Kong Polytechnic University. A study design overview is shown in **Figure 1**.

2.2 Identification of the evidence base

Research evidence from five systematic reviews were utilized to identify the evidence base [12, 15-18]. One systematic review summarizing research evidence on AT for CINV management was used to inform the AT protocol development including the commonly used auricular acupoints and AT modality [12]. Another systematic review on the safety of AT was employed to identify the most convenient AT modality

with less and mild adverse events [16]. While the other three systematic reviews on sham acupoint stimulation design were further adopted to guide the development of a sham AT intervention [15, 17, 18].

2.3 Identification of the AT theories and practice standards

The homuncular reflex theory and *zang-fu* organs and meridian theory [10, 11, 19, 20] were utilized to further provide theoretical rationale to support the selected ear acupoints. AT practice standards developed by Abbate (2004) [19], Guan, et al. (2002) [21], Huang (2001) [22], and Oleson (2014) [23], and recommendations from other AT/acupuncture practitioners, were further adopted to provide practice rationale of the selected AT modality, acupoint formula, AT treatment duration and sessions, and the technique and intensity of acupoint stimulation. The standard ear acupoints chart — *Nomenclature and Location of Auricular Points* [24] was utilized to guide the accurate location of the selected acupoints.

2.4 Identification of the CINV symptom characteristics

Characteristics of the CINV symptoms, including the onset and duration of acute and delayed emesis, and the involved *zang-fu* organs, were considered as supporting evidence to determine the selected AT acupoint formula and the appropriate duration of AT intervention.

2.5 Validation of the AT protocol via a content validity study

A preliminary AT protocol developed following the above procedures was further assessed by a panel of experts specialized in AT and integrative oncology through a content validity study to identify its scientific and practical appropriateness. The content validity index (CVI) was utilized to determine panel's sample size and consensus. To achieve a satisfactory CVI of 0.83 for each assessment item within the preliminary AT protocol, six experts would be required [25]. A purposive sampling method was utilised for expert recruitment. To be eligible for the expert panel, the panel participants would need to be registered health practitioners or academics, have been working in the research and practice areas of integrative oncology and AT for at least ten years, and hold a senior clinical or academic position at the level of associate consultant, principal research fellow, or associate professor or above.

Panel experts were recruited through the research team's professional network. The content validity assessment form consists of a true AT intervention protocol and a sham AT intervention protocol, and each protocol was described in five items for the experts' rating, including: **(1)** selected auricular acupoints; **(2)** AT modality; **(3)** AT technique; **(4)** AT frequency and sessions; **(5)** AT total duration. Each item was independently evaluated on a 4-poin Likert scale ranging from 1 ("totally inappropriate") to 4 ("very appropriate"). For items rated below 3, comments and suggestions with relevant evidence (references) were encouraged to help further refine the AT intervention protocol.

The CVI was used to identify the content validity for each item (item-level CVI) and the entire protocol (scale-level CVI) [25, 26]. A satisfactory item-level CVI was determined as no less than 0.83 which means at least five out of six experts scored the item as 4 ("very appropriate") or 3 ("appropriate") [25, 26]. While the scale-level CVI was estimated by the proportion of items scored as "4" or "3", and a satisfactory level was determined as no less than 80% [25, 27]. If satisfactory CVI could not be achieved at the first round, the AT protocol would be further refined according to the suggestions and evidence provided by the panel, and further rounds of assessment would continue until the pre-defined CVI was reached.

3 Results

3.1 The true AT intervention protocol

Development of the true AT intervention consists of the following procedures: **(1)** selection and location of auricular acupoints; **(2)** selection of appropriate AT modality; **(3)** identification of appropriate intensity and technique of AT; **(4)** identification of appropriate frequency, sessions and total duration of AT. Details of the true AT intervention protocol with relevant supporting evidence are presented in **Table 1**.

3.1.1 Selection and location of auricular acupoints

The homuncular reflex theory and *zang-fu* organs and meridians theory hold a common belief that pathological conditions occurred in specific body parts would have their correspondence to certain ear acupoints [10, 11, 19]. CINV symptoms are generally attributed to the dysfunctions in the *zang-fu* organs of stomach (including cardia), spleen, and liver [28-32]. Following the two AT theories and the principle of "*selection of auricular acupoints corresponding to the afflicted parts*" [22] (pp. 265-272),

"stomach (CO_4)," "cardia (CO_3)," "spleen (CO_{13})," and "liver (CO_{12})" were identified as the targeted acupoints for CINV alleviation. In accordance with the principle of "*selection of auricular acupoints according to the effects of acupoints*" [22] (pp. 265-272), another three acupoints— "*shenmen* (TF_4)," "sympathetic (AH_{6a})," and "subcortex (AT_4)", were further selected given their potential in regulating gastrointestinal activities [10, 21, 22]. The seven acupoints were also supported by systematic review findings as the commonly used acupoints for relieving CINV [12]. The standard ear acupoints chart — *Nomenclature and Location of Auricular Points* [24] was used to identify the accurate locations of the selected acupoints. As supported by systematic review evidence and relevant AT practice standards [12, 21, 23], an auricular acupoint detector was employed to help precisely locate the targeted acupoints by measuring the altered electrical resistance of the local skin at the selected acupoints.

3.1.2 Selection of appropriate AT modality

Selection of the appropriate AT modality was supported by research evidence derived from two systematic reviews [12, 16]. Auricular acupressure as a non-invasive AT modality was selected as an appropriate method given its popularity for CINV management and superiority to invasive AT methods in terms of risk-benefit balance, practice safety, and convenience [12, 16]. Compared with invasive AT methods, auricular acupressure has been proved to be associated with only mild, transient, and well-tolerated side reactions [16]. Once trained by qualified practitioners, patients can also self-practice ear acupressure without frequent visits to healthcare services [33]. Vaccaria seeds ("*wang bu liu xing zi"*) were identified to be an appropriate medium for performing ear acupressure given their optimal physical features (density, texture and size) for creating strong and constant acupoint stimulation to achieve satisfactory AT treatment effects [19]. Meanwhile, considering that regular tapes for attaching the acupressure seeds to the ear skin may contribute to some local skin reactions like redness and discomfort [16], hypoallergenic tapes were therefore used in this AT protocol to minimize the potential adverse events.

3.1.3 Identification of appropriate intensity and technique of AT

Intensity of acupoint stimulation was determined by the achievement of *deqi* sensation when performing acupressure. *Deqi* is a Traditional Chinese Medicine (TCM) term to indicate the achievement of satisfactory therapeutic effects of acupoint stimulation [22], which is usually described as a local sensation of soreness, heaviness, tingling, heat and minor aching at the stimulated acupoint site [21, 34, 35], and is commonly used in AT research [12]. The technique for self-acupressure follows Guan, et al.'s AT practice standards [21]: placing index finger and thumb at the interior and exterior of the auricle, respectively, where the targeted acupoint is located, and then gradually pressing the taped seed until the occurrence of a sensation of soreness, heaviness, tingling, or distension (the achievement of *deqi)*; immediately after reaching the *deqi* sensation, slightly moving the fingers around the acupressure area to locate a sensitive point with the most obvious sensation of *deqi* and continuing with the acupressure on that point for 20 to 30 seconds.

3.1.4 Identification of appropriate frequency, sessions and total duration of AT

Relevant AT practice standards [21, 22] and the CINV symptom characteristics were utilized to identify the appropriate AT treatment frequency, sessions and total duration. The standard frequency of AT treatment was scheduled as three times per day [21, 22], with each time lasting around four to seven minutes for pressing all the bilateral acupoints. Acupressure should be daily performed in the morning, afternoon, and evening for the first five days of the chemotherapy cycle, regardless of whether patients had experienced nausea and vomiting or not. Apart from the regular daily acupressure, this study also adopted the systematic review evidence [12] that patients can have additional acupressure as soon as they feel nauseous. Total duration of AT treatment is usually determined by the nature of the treated health condition [21], and the length of AT treatment was therefore identified by following the general progress of nausea and vomiting after receiving the most recent chemotherapy. In cancer patients undergoing chemotherapy, the nausea and vomiting often last 120 hours (five days) after receiving the chemotherapeutic agents [36, 37]. Therefore, the total AT treatment duration was designed as five days during the chemotherapy cycle. One treatment course was deemed adequate as the taped seeds can usually stay on the selected acupoints for up to seven days if properly protected [22].

3.2 The sham AT intervention protocol

The sham AT intervention was developed based on evidence adopted from three systematic reviews on sham acupoint stimulation [15, 17, 18]. To achieve a successful blind design between the true and sham AT interventions in the future clinical trial, the selected acupoints in the sham intervention were the same as those in the true AT protocol. To avoid any specific therapeutic effects produced by acupoint stimulation, no acupressure was scheduled in the sham AT, and relevant acupressure seeds were replaced by Junci Medulla ("*deng xin cao*"). Details of the sham AT intervention protocol with relevant supporting evidence are presented in **Table 2**.

3.2.1 Identification of appropriate sham acupoints

Three types of sham acupoints are commonly utilized in research, including non-acupoints, irrelevant acupoints to the conditions being treated, and the same acupoints (as in the true intervention) with inadequate stimulation [15, 17, 18]. Non-acupoints are inactive points located near the true acupoints, which make them an appropriate option in body acupoint stimulation studies for achieving a satisfactory blind design [15, 17]. However, non-acupoints might not be appropriate in AT research given hundreds of active acupoints are concentrated in the small auricle, which makes it extremely difficult to locate any inactive points near the true acupoints. Many AT studies utilized non-acupoints located at the ear helix as the sham comparison [38-41], which is problematic for maintaining blind design in this study given that the majority of the targeted acupoints were centrally located around the helix crus and in the cymba concha and cavum concha.

Acupoints which are irrelevant to the conditions being treated are commonly utilized as sham interventions but these might not be an appropriate placebo design given the holism philosophy in acupoint stimulation theories that stimulation of any active acupoints could evoke some biological reactions of the immune, endocrine, cardiovascular and nervous systems [42], which might contribute to some effects on the treated health conditions. Meanwhile, blind designs could be problematic when utilizing irrelevant acupoints as the sham comparison considering the totally different acupoint locations between the true and sham intervention. Given all the above concerns, the sham AT acupoints utilized in this study were determined as the same as in the true AT intervention to achieve a successful blind design between the true and sham AT interventions.

3.2.2 Identification of appropriate intensity, technique, and treatment dosage of sham AT

Using the same acupoints as in the true intervention with light stimulation or without any stimulation has been commonly applied as an appropriate sham comparison design [15, 17, 42, 43]. The sham AT intervention in this study followed the same design to schedule no manual acupressure to the acupoints to minimize potential treatment effects evoked from constant stimulation. The acupressure tape used in the sham AT intervention was also replaced by Junci Medulla ("*deng xin cao*") which is soft in texture and is unable to produce sufficient acupoint stimulation to evoke therapeutic effects. Junci Medulla has been used in AT research as a sham AT comparison [44]. The appearance of the sham acupressure tape was identical to the ones used in the true AT. The total treatment duration of the sham AT intervention was the same as the true AT intervention, which was five days from day 1 to day 5 of the chemotherapy cycle.

3.3 Validation of the AT intervention protocol

Six experts specialized in AT and integrative oncology from the United States and China were invited to determine the content validity of the AT intervention. All the experts had more than 10 years of professional experience in the areas of AT and integrative oncology, and half of the experts had over 20 years of experience. Three held a joint senior appointment of university academic and hospital clinicians and predominantly worked in the university hospital, while the other three predominantly worked as university academics with clinical practice commitment as part of their clinical teaching and research roles. Characteristics of the expert panel are presented in **Table 3**. The content validity assessment was conducted for one round only given satisfactory CVI for both item-level and scale-level were achieved after the first round of evaluation. **Table 4** presents the convent validity assessment results. All the items within the true and sham AT protocols were identified as content valid with the item-level CVI ranging from 0.83 to 1.0, and the scale-level CVI reaching 1.0.

4 Discussion

This study follows the MRC framework to successfully develop an evidence-based AT intervention for CINV management in cancer patients. The intervention development process comprehensively adopted systematic review research evidence, AT theories and practice standards, cancer symptom characteristics, and expert panel consensus to ensure the intervention is research-informed, theoretically appropriate and practically feasible, which is rarely utilised in the field of complementary medicine and integrative oncology. The entire methodological procedures presented in this study can provide implications for future research in developing complex interventions that are standardized and tailored to specific health condition and are supported by well-justified research evidence, theoretical rationale and practice standards.

Systematic review findings provide research evidence to support the intervention protocol development [14]. Three of the five systematic reviews utilized in this study were completed by our team given that no study had ever been conducted to summarise the research evidence on AT for CINV management, the safety of AT, and the strength and limitations of sham acupressure design. The first systematic review [12] provided key evidence to identify the most commonly used AT modality and acupoint formula for CINV management, with strong theoretical rationale supported by relevant AT theories and practice standards. A combination of research evidence and theories and practice standards ensures that the AT protocol is research-informed and theoretically and practically appropriate, which is one of the distinguished features of this study that has rarely been utilized in the field of complementary medicine. While another feature is to adopt the cancer symptom characteristics to inform the AT treatment duration. This study followed the general progress of CINV symptoms [36, 37] to ensure a sufficient AT duration to cover the general CINV symptom period but also avoid unnesscarily prolonged intervention to reduced patients' burden.

Cancer patients with chemotherapy can be very vulnerable to invasive interventions given their compromised immune functions. It is therefore important to identify an AT intervention that is less invasive with less adverse events. Although invasive acupoint stimulation methods can produce larger effects than non-invasive approaches [45], a balance between the benefit and risk, and convenience for self-practice, should be considered when designing the AT intervention for CINV management. This study adopted the systematic review evidence [12, 16] to determine ear acupressure as an optimal AT modality given its promising role in relieving CINV and superiority to other invasive AT methods in terms of safety. Using systematic review evidence to inform the potential adverse events and relevant management strategies of the complex intervention is the third distinguished features of this study.

Inappropriate sham acupoint stimulation design may contribute to unwanted specific effects which can lead to an overestimation of the "placebo" effects of the sham intervention [17] and subsequently compromise the research design with a misleading judgment of the causality between the interventions and outcomes. This study adopted research evidence from three large systematic reviews [15, 17, 18] to identify an optimal sham AT design. Using the same acupoints as in the true intervention without any acupressure can minimize acupressure-induced specific treatment effects. While the same acupoints utilized in both protocols can also achieve a blind design between the true and sham AT intervention, although the absence of acupressure in the sham AT intervention may let some patients distinguish the difference between study arms. Relevant strategies were proposed in the study phase II (pilot randomised controlled trial) to minimise the risk of "breaking the blind", such as recruiting AT-naïve participants, and arranging separate wards for participants allocated to different study arms. In addition, a standard care comparison without any AT intervention was also designed in the study phase II as the third group of the pilot trial to identify the size of the placebo effects of sham AT through a comparison of the CINV outcome effect sizes between the sham AT group and the standard care group.

Excellent content validity of the AT intervention was demonstrated among the expert panel to well support its theoretical and practical appropriateness. However, one of the panel members held different opinion regarding the sham AT design. The expert pointed out that vaccaria seeds and Junci Medulla used in the true AT and sham AT, respectively, can contribute to significant variations, and further recommended to use vaccaria seeds in both interventions. After a discussion among the research team members, no further modification was made to the sham AT intervention given that vaccaria seeds would produce constant stimulation to the acupoints even without any manual acupressure and pose a great risk for the sham AT intervention to generate specific treatment effects on CINV. All of which can considerably impede the value

of the sham AT design that aimed to explore the placebo effects of the sham intervention when compared with the standard methods of care as well as distinguish the specific therapeutic effects of AT from its non-specific (placebo) effects when compared with the true AT intervention.

This study has some limitations. Identification of the AT intervention frequency and duration was purely based on the AT practice standards and CINV symptom characteristics but not the systematic review evidence. The unsatisfactory methodological quality and outcome measures of the included studies in the first systematic review led to an absence of meta-analysis and sub-group comparison to identify the most effective AT treatment duration and frequency [12]. Meanwhile, the lay experts—breast cancer patients were not included in the expert panel to evaluate the content validity of the AT intervention from the end users' perspective, and the purposive sampling method for expert recruitment may also affect the representativity of the panel. Nevertheless, the AT intervention developed through the MRC framework phase I can only be regarded as a preliminary protocol which needs to be tested in a pilot clinical trial (MRC framework phase II) to further confirm its utility, feasibility and acceptability in clinical research settings.

5 Conclusion

This study followed the MRC framework to successfully develop an evidence-based AT intervention for CINV management which is well supported by systematic review evidence, AT theories and practice standards, cancer symptom characteristics, and expert panel consensus. The preliminary AT intervention would then be further evaluated in a pilot randomised controlled trial to confirm its utility, feasibility and acceptability in clinical settings.

List of abbreviations

AT: Auricular therapy
CINV: Chemotherapy-induced nausea and vomiting
MRC: Medical Research Council
CVI: Content Validity Index

Declarations

Ethics approval and consent to participate

This study was approved by the Human Subjects Ethics Sub-Committee at The Hong Kong Polytechnic University.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Conflict of interests

The authors declare that they have no competing interests.

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Authors' contribution

JYT led the study conception and design, implemented the study, analysed and interpreted the study data, and drafted and revised the manuscript; **JL** supported the study conception and design, assisted with the study implementation, and revised the manuscript; **LKS and AM** supported the study conception and design and revised the manuscript; **TW** supported the study implementation and revised the manuscript.

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