An evidence-based somatic acupressure intervention for managing the breast cancer fatigue-sleep disturbance-depression symptom cluster: Development and validation following the Medical Research Council framework

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Abstract

Background

Somatic acupoint stimulation (SAS) has been frequently utilised as a promising intervention for individual cancer-related symptom management such as fatigue, sleep disturbance and depression. However, research evidence regarding the role of SAS in mitigating the fatigue-sleep disturbance-depression symptom cluster (FSDSC) has been scant. This study was conducted to develop an evidence-based SAS intervention protocol that can be further implemented in a Phase II randomized control trial (RCT) to manage the FSDSC in breast cancer survivors.

Methods

The Medical Research Council Framework for Developing and Evaluating Complex Intervention (MRC framework) was employed to guide the development procedures of the SAS intervention protocol, including identification of existing evidence base; identification of theories and practice standards; and validation of the SAS intervention protocol. A content validity study was performed through an expert panel to assess the scientific and practical appropriateness of the SAS intervention protocol. The content validity index (CVI), including item level-CVI and protocol-level CVI, were calculated to evaluate the consensus level of the expert panel.

Results

Key components of SAS protocol, including acupoint formula, SAS modality, technique, intensity and frequency, were identified for both a true and a placebo SAS intervention based on the best available research evidence retrieved from systematic reviews and clinical trials, relevant theories particularly the inflammatory process, yin-yang theory, and zang-fu organs and meridians theory, and acupressure practical standards. The true SAS intervention was determined as a daily self-administered acupressure on specific acupoints for seven weeks. The placebo SAS was designed as light acupressure on non-acupoints with the same frequency and duration as the true SAS. Excellent content validity was achieved after one round of expert panel assessment, as all the key components of the true and placebo SAS protocols were rated as content valid (CVI ranged from 0.86 to 1.00).

Conclusion

A research-informed, theory-driven and practically feasible SAS intervention protocol for the FSDSC management in breast cancer survivors was developed following the MRC framework. The feasibility and acceptability of the SAS intervention will be further tested in breast cancer survivors through a Phase II RCT.

1. Background
Fatigue is one of the most common symptoms in breast cancer survivors (BCS) throughout their illness trajectory [1]. Around half of the BCS experience significant fatigue before the anticancer treatment, and the prevalence was reported to be even higher during the posttreatment period, with the incidence ranging from 64% to 75% [2-4]. Sleep disturbance and depression are another two frequently reported symptoms among BCS at posttreatment stage, with the incidence of 47% to 65% and 25% to 39%, respectively [2,5-7]. Fatigue, sleep disturbance and depression do not present as an isolated condition but often co-occur as a symptom cluster [8] which is defined as “three or more concurrent symptoms that are related to each other” (p. 465) [9]. Fatigue, sleep disturbance and depression are interrelated, and fatigue has been identified as the core symptom as it can predict the other two symptoms [8, 10]. The fatigue-sleep disturbance-depression symptom cluster (FSDSC) can negatively impact cancer survivors’ physical and psychological well-being, deteriorate their quality of life and immunity, lead to various complications, and increase financial burden as well as healthcare utilization, all of which can subsequently reduce cancer survivors’ compliance to treatment and even decrease long-term survivals [8, 11-15].

Due to the complex mechanisms of cancer symptom cluster, no tailored pharmaceutical agents have been proposed yet for FSDSC management [13]. Contradictory treatment effects have been found for many pharmaceutical agents such as melatonin and paroxetine [13, 16,17]. Meanwhile, drug-related adverse effects and the potential drug interactions with concurrent anticancer regimens [14, 16, 18, 19] also limit the level of evidence and recommendation of pharmacological interventions for FSDSC management. Excessive use of pharmaceutical agents may further worsen cancer survivors’ chemical and financial burden. Therefore, there is a strong need to explore the role of non-pharmacological methods for cancer symptom cluster management as adjuvant approaches to pharmaceutical agents.

Several non-pharmacological approaches, such as cognitive behavioural therapy (CBT), physical exercise and yoga, have been used for cancer symptom management with demonstrated beneficial effects [1,13,20,21]. However, those non-pharmacological interventions were mainly focused on managing individual symptom but not the entire symptom cluster. Feasibility issues of some non-pharmacological approaches have also been a concern. For instance, CBT and yoga usually require extensively professional support, and survivors may need frequent travels to particular settings for intervention, which can be considerably time- and energy-consuming. Professional-supervised interventions also limit the space for long-term home-based self-management of cancer symptoms. Physical exercise may induce potential recruitment bias as fatigue can hinder study participation in research involving exercise training [11]. Considering the long-term experience of FSDSC in BCS, other home-based non-pharmacological interventions that can be self-managed by survivors are worthy of further exploration.

Somatic acupoint stimulation (SAS), including body acupuncture and acupressure, has been frequently utilised to manage various health conditions. Existing evidence supports a promising role of SAS in individual symptom management of cancer-related fatigue, sleep disturbance and depression [19,22,23,24,25,26], although robust evidence has been inconclusive due to unsatisfactory methodological quality and limited sample size identified in some studies. Meanwhile, the intervention protocols of SAS, including acupoint formula, stimulation technique, frequency, and duration, have also
varied significantly across studies [22,25]. A SAS protocol with evidence-based optimal intervention dosage and acupoint formula has been lacking, and no studies on SAS have ever been conducted for FSDSC management. This study was therefore conducted with the aim of developing and validating an evidence-based SAS intervention for FSDSC management in BCS.

2. Methods

The abstract of this manuscript has been accepted and presented in the Multinational Association for Supportive Care in Cancer (MASCC)/ International Society for Oral Oncology (ISOO) 2022 Annual Meeting, Toronto, Canada.

2.1 Study design

The study procedures follow the *Medical Research Council Framework for Developing and Evaluating Complex Intervention* (MRC framework), which outlines a “development-evaluation-implementation” framework for establishing an evidence-based complex intervention with four design phases [27]: 1) phase I: developing the intervention protocol; 2) phase II: examining the intervention feasibility and piloting its methodological procedure; 3) phase III: evaluating the interventional effects; and 4) phase IV: utilising and disseminate the intervention. This study followed phase I of the MRC framework to develop and validate an evidence-based SAS intervention protocol which included three major components: 1) identification of existing research evidence; 2) identification of relevant theories and practice standards; and 3) validation of the intervention protocol. This study is the phase I study of a large research project examining the value of acupressure for symptom management in early-stage BCS. Ethical approval of the project was granted by the Human Research Ethics Committee at Charles Darwin University in Australia (H19017). Procedures of the current study are presented in Fig.1.

2.2 Study procedures in developing and validating the SAS intervention protocol

2.2.1 Identification of existing research evidence base

The MRC framework suggests that an appropriate intervention should be systematically developed based on reliable evidence that is identified in research literature and relevant theories [27]. In this study, findings from six systematic reviews and three clinical trials [30-32] were adopted to identify the relevant research evidence base. Of the six systematic reviews, three (one was published [28] and other two were under review) on SAS for FSDSC management in cancer patients (each review focused on one single symptom within the FSDSC) were conducted by our research team, while another three systematic reviews on safety issue of acupressure [29] and placebo acupoint stimulation design [33,34] were utilised to inform the selection of appropriate SAS modality and the development of a placebo SAA group, respectively.

2.2.2 Identification of relevant theories and practice standards

The MRC framework emphasises the importance of utilising appropriate theories to guide the design of an intervention by clarifying the potential mechanism regarding the effectiveness of the proposed
intervention [35, 36]. A comprehensive literature search was therefore conducted to locate appropriate theories to support the use of SAS for cancer symptom management. Databases including PubMed, Google Scholar, and China National Knowledge Infrastructure (CNKI) were searched using “acupressure”, “acupuncture”, “acupuncture stimulation”, “theory”, and “fatigue”, in combination with manual search of books on Traditional Chinese Medicine through the university library. Neurophysiological theories and some TCM theories, particularly the inflammatory theory, yin-yang theory, and zang-fu organs and meridians theory, were identified and utilised to theoretically clarify the potential mechanisms regarding FSDSC in BCS and to inform the selection of appropriate intervention. Practice standards and handbooks of acupuncture stimulation [37,38] were also used to provide rationale regarding the selection of acupoints, modality, intensity and technique, and dosage of the SAS treatment.

2.2.3 Validation of the SAS intervention protocol

The MRC Framework suggests that the context in which the intervention will take place should be considered when developing an intervention [27]. A content validity study was conducted through a panel of experts to assess the scientific and practical appropriateness of the SAS intervention protocol. The panel consensus was determined by using the content validity index (CVI) [39]. A panel of seven experts were established. According to Lynn [39], a satisfactory CVI for each assessment item within an intervention protocol must be at least 0.86 when there are seven experts, which indicated that at least six experts in the panel should agree that the item is content valid [39]. Experts were those who meeting the following inclusion criteria: 1) were registered health practitioners or academics; 2) had more than 10 years of research and/or practice experience in the field of oncology, TCM and/or acupuncture stimulation; 3) had a senior academic or clinical position (associate physician, associate professor or above); and 4) were willing to be involved in the content validation study.

All the panel experts were recruited through a purposive sampling approach. The form of content validity assessment includes two parts: the true SAS protocol and the placebo SAS protocol. Each protocol had five items for assessment, namely “the acupoints formula”; “the SAS modality”; “the SAS intensity and technique”; “the SAS frequency and session”; and “the SAS total duration”. Each item was assessed using a 4-point Likert scale (from 1= “totally inappropriate” to 4= “very appropriate”). Comments and suggestions were requested from the panel when the item was rated as “totally inappropriate” or “inappropriate” to assist with the further refinement of the protocol.

Content validity of each item (Item level CVI, I-CVI) and entire protocol (scale level CVI, S-CVI) were assessed [39,40]. Given that a satisfactory I-CVI should be no less than 0.86, at least six out of the seven experts in this study should rate the item as “appropriate” or “very appropriate” [39]. The S-CVI was the proportion of items that achieved a satisfactory I-CVI, and a satisfactory S-CVI should be at least 0.9 [41]. Items with unsatisfactory CVI should be further revised until a satisfactory CVI values were achieved.

3. Results

3.1 True SAS intervention protocol
The true SAS intervention protocol was developed through the following four procedures: 1) selecting appropriate SAS intervention and acupoints formula; 2) selecting appropriate SAS modality; 3) identifying appropriate SAS intensity and technique; and 4) identifying of appropriate SAS dosage. Table 1 summarises the contents of the true SAS intervention protocol, as well as relevant justifications and evidence source.

Table 1 Contents of the true SAS intervention protocol with relevant justifications and evidence
<table>
<thead>
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<th>Details</th>
<th>Justifications</th>
<th>Sources of evidence</th>
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<td>• TCM theories: <em>yin-yang</em> theory, and <em>zang-fu</em> organs and meridians theory [43, 47,48]</td>
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<td></td>
<td>• Sanyinjiao (SP6)</td>
<td>distress and depression</td>
<td>• SAS practical standards: instructions of function and clinical usage of somatic acupoints [37,38]</td>
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<td></td>
<td>• Taixi (KI3)</td>
<td>• Commonly utilised acupoints for alleviating cancer-related fatigue, sleep</td>
<td>• Systematic review evidence [28*]</td>
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<tr>
<td></td>
<td>• Hegu (LI4)</td>
<td>distress and depression</td>
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<td>• Neiguan (PC6)</td>
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<td>• Shenmen (HT7)</td>
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<td>• Baihui (GV20)</td>
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<td>• Qihai (CV6)</td>
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<td>• Guanyuan (CV4)</td>
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<td>• Yintang (EX-HN3)</td>
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<td>SAS modality</td>
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<td>• Systematic review evidence [28*, 29]</td>
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<td></td>
<td>• Superiority to invasive acupuncture regarding safety and convenience in</td>
<td>• Clinical research evidence [30-32]</td>
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<td></td>
<td>facilitating self-management in the long run</td>
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<tr>
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<td>• “Deqi” sensation: a key indicator of the achievement of satisfactory therapeutic</td>
<td>• Systematic review evidence [28*]</td>
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<td></td>
<td>• Technique: Survivors self-administrated manual acupressure using</td>
<td>effects of SAS</td>
<td>• SAS practical standards [30,49, 50]</td>
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<td></td>
<td>finger pressing</td>
<td>• Acupressure via finger: a common approach of self-acupressure with</td>
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<td>demonstrated safety and convenience for self-practice</td>
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<td>SAS frequency, sessions and</td>
<td>• A daily SAS for seven weeks, with each session lasting 36 min (2 min</td>
<td>• Commonly used SAS dosage in both research and practice with demonstrated</td>
<td>• Systematic review evidence [28*]</td>
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<tr>
<td>total duration</td>
<td>on each acupoint)</td>
<td>benefits for individual symptom alleviation, appropriate feasibility and</td>
<td>• SAS practical standards [51]</td>
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<td></td>
<td></td>
<td>acceptability</td>
<td>• Clinical research evidence [30]</td>
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</table>

SAS: Somatic acupoint stimulation; * The systematic review evidence was adopted from three systematic reviews that were conducted by our research team, with one published and two under review: (1) Wang, T., Tan, JY., Yao, LQ., et al. Effects of somatic acupoint stimulation on anxiety and depression in cancer patients: an updated quantitative synthesis of randomized controlled trials. Manuscript submitted for publication; (2) Tan, JY., Wang, T., Kirshbaum MN, et al., Somatic acupoint stimulation for cancer-related
fatigue: A quantitative synthesis of randomized controlled trials. Manuscript submitted for publication). Only the published systematic review [28] was included in the reference list.

3.1.1 Selecting appropriate SAS intervention and acupoints formula

Neurophysiological theories particularly the inflammatory theory, and some TCM theories including the *yin-yang* theory and the *zang-fu* organs and meridians theory were used to describe the potential mechanism of SAS for FSDSC management in BCS. Inflammation has been regarded as the key biological pathway of FSDSC as the inflammatory cytokines can result in fatigue (the core symptom of the FSDSC) via the autonomic nervous system and/or the Hypothalamic-pituitary-adrenal axis [11,42]. An increase of inflammatory markers can also affect immune regulation and recovery via the cellular immune system [11]. Current evidence has demonstrated an important role of acupoint stimulation in decreasing the inflammatory cytokines and modulating the immune functions [43]. Such potential biological mechanisms of acupoint stimulation involving the regulation of inflammatory cytokines highlight its promising role for FSDSC management given that the development of cancer symptom is believed to be closely linked with the inflammatory responses induced by inflammatory cytokines [2].

The TCM believes that the main pathogeneses of FSDSC are the imbalance between *yin* and *yang*, and deficiencies of *qi* [44,45]. Imbalance between *yin* and *yang* can negatively affect the operation of *qi* and meridians and subsequently distort the normal *zang-fu* organ functions given that each major meridian is closely associated with specific *zang-fu* organs (heart, liver, spleen, lungs and kidney). *Qi* refers to the vital energy of the body, which can maintain blood circulation, warm body, and fights diseases [46]. *Qi* deficiency can significantly contribute to a range of deficiency syndromes in cancer patients including fatigue [46]. Acupoints are the areas where the *qi* of *zang-fu* organs and medians are transfused [43]. According to the *yin-yang* theory and the *zang-fu* organs and meridians theory, stimulating specific acupoints can promote the flow of *qi of the body* to maintain blood circulation, dredge the meridians, balance *yin* and *yang*, and regulate *zang-fu* functions [43, 47,48].

In accordance with the TCM theories and the relevant acupoint stimulation practice standards/handbooks regarding the indications, effects and roles of somatic acupoints [37,38], eleven acupoints were selected to use in the intervention protocol, which include Zusanli (ST36), Sanyinjiao (SP6), Taixi (KI3), Hegu (LI4), Neiguan (PC6), Shenmen (HT7), Baihui (GV20), Qihai (CV6), Guanyuan (CV4), Yintang (EX-HN3), and Taichong (LR3). Selection of these acupoints was also supported by our systematic reviews as the commonly utilised acupoints for alleviating the symptom of cancer-related fatigue, sleep distress and depression with demonstrated benefits for symptom improvement (details see Table 1). Two practice standards/handbooks of acupoints stimulation [37,38] were used to inform the accurate location of each acupoint included in the protocol. Details of the indications, effects and roles of each of the selected acupoints are listed in the Supplementary File.

3.1.2 Selecting appropriate SAS modality
Considering that the SAS has two modalities- somatic acupuncture and somatic acupressure, evidence from systematic review findings and clinical trials [28, 29-32] were adopted to support the selection of an appropriate SAS modality. Due to the popularity of somatic acupressure for symptom management in cancer population and its superiority to invasive somatic acupuncture regarding the risk-benefit balance, convenience, and safety [29-32], the non-invasive somatic acupressure was identified as an appropriate SAS modality. Comparing with somatic acupuncture which is administered by qualified practitioners and is an invasive method with potentially severe adverse effects, the non-invasive somatic acupressure can be a safe method for self-management of cancer symptoms long-term.

3.1.3 Identifying appropriate SAS intensity and technique

Deqi sensation as a key indicator of the achievement of satisfactory treatment effects of acupoint stimulation has been widely utilised in research and practice [28, 49]. Deqi usually refers to a local sensation of dull pain, aching, sore, numb, distended, heavy, electric, throbbing, and warmth [49]. In this study, the acupoints stimulation intensity was determined via using the indicator of deqi sensation. For the self-acupressure technique, practice standards of finger acupressure were adopted, which include the skills of pointing, pressing, and kneading. Pointing is the patients locating the acupoint [30,50]. Pressing is the patients using either thumb or index finger to press the point to evoke the deqi sensation [50]. Kneading is the patients rotating their thumb or index finger on the identified acupoint to achieve the therapeutic effects [50].

3.1.4 Identifying appropriate SAS dosage

The SAS dosage, including frequency, session and total duration, was determined based on the standards of acupressure [51], and research evidence from systematic reviews and high-quality clinical trials [28, 30]. The frequency of SAS treatment was commonly scheduled as daily, with acupressure performing on each acupoint for two to three minutes [51]. Considering that eleven acupoints were selected in this study and seven of which were bilateral acupoints, it was determined that each acupoint should be pressed for two minutes to minimize participants’ burden. For the total duration of SAS, clinical research has well documented that a minimal of four-week daily acupressure is required to achieve satisfactory effects and a seven-week daily acupressure to achieve maximum effects on cancer-related fatigue alleviation (the core symptom of FSDSC) [30]. Considering all the evidence mentioned above, the SAS dosage in this study was scheduled as a daily acupressure for seven weeks, with each acupoint been pressed for two minutes.

3.2 Protocol of the placebo SAS intervention

The placebo SAS intervention protocol was developed based on the evidence extracted from two comprehensive systematic reviews on placebo acupoint stimulation design [33, 34]. To promote the success of a satisfactory blind design in future RCT and to minimize the potential treatment effects of the placebo acupressure, non-acupoints located one to three cm away from the active acupoints utilised
in the true intervention but away from the meridians [33] were selected as the placebo acupressure points. The number of the non-acupoints was same as that of the true SAS intervention.

3.2.1 Identifying appropriate placebo acupoints

A few placebo acupoints designs are commonly utilised in clinical research, which include non-acupoints, true acupoints (but unrelated to the targeted health problem), and the same acupoints as used in the true group with light or no stimulation [33,34]. Given that our future RCT will implement a blind design of participants between the true and placebo acupressure groups, true acupoints with light or no stimulation might not be an appropriate design to achieve a successful blind design, particularly for participants with previous experience of acupressure [33]. Meanwhile, research evidence has indicated that even light acupressure at the true points can evoke some therapeutic effects for symptom alleviation such as pain [52]. Irrelevant acupoints (to the targeted health condition) are another commonly adopted placebo acupoint stimulation approach. However, according to the “holism concept” of TCM, stimulation of any acupoint could lead to a comprehensive response of the human body and subsequently create some treatment effects, particularly when participants in true and placebo group receiving a same acupressure intensity [33,53]. Non-acupoints are defined as inactive points that located near the true acupoints but away from the meridians [33,34]. Non-acupoints have been the most commonly utilised placebo approach in acupoint stimulation studies as this method would theoretically avoid evoking any specific therapeutic effects generated from true acupoint stimulation. Non-acupoints located near true acupoints are also considered as an appropriate design for maintaining a successful blind design [33]. Given together, the non-acupoints approach was identified as the placebo SAS method in this study. The number of non-acupoints was same in the true intervention. All the selected non-acupoints were suited one to three cm away from the active acupoints used in the true intervention but away from the meridians [33].

3.2.2 Identifying appropriate placebo SAS intensity, technique, frequency, session and total duration

Using acupressure device has been recommended as an appropriate method to achieve satisfactory blind design, particularly when the devices in true and placebo group are identical [33]. However, many acupressure devices such as acupressure band are only applicable for acupoints located on arms and legs. Given that some of the selected acupoints in this study are on head and abdomen, it was unrealistic to use acupressure device on such acupoints. Finger acupressure on the non-acupoints was therefore applied for placebo intervention in this study.

Placebo acupressure using a same intensity as in the true acupressure intervention may secure a successful blind design. However, there are over 2000 extra-points currently identified in human body which are not linked with the meridians [53]. Therefore, it might be possible that some so-called non-acupoints are potentially active acupoints with specific treatment effects [53]. To minimize the potential therapeutic effects of placebo SAS intervention to the greatest extent, light acupressure on non-acupoints without evoking the deqi sensation was utilised in this study. Frequency, session and total duration of the
placebo intervention were scheduled the same as the true intervention (a daily placebo acupressure for seven weeks, with each acupoint been lightly pressed for two minutes).

3.3 Content validity of the SAS intervention protocol

Seven experts in the field of oncology, TCM and/or acupoint stimulation were recruited to evaluate the content validity of the proposed SAS intervention protocol. Basic information of the expert panel is shown in Table 2. Satisfactory I-CVI and S-CVI were achieved after one round of assessment. All the five items presented in the true and placebo SAS protocol were determined to be content valid (I-CVI ranged from 0.86 to 1.00 and S-CVI was 1.00). Details of the content validity assessment are presented in Table 3.

Table 2 Basic information of the expert panel (N=7)

<table>
<thead>
<tr>
<th>Basic information of the expert panel</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Working institution</strong></td>
<td></td>
</tr>
<tr>
<td>• University</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>• Hospital</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
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<tr>
<td>• 30-40 years old</td>
<td>3 (42.9%)</td>
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<tr>
<td>• 40-50 years old</td>
<td>2 (28.5%)</td>
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<tr>
<td>• 50-60 years old</td>
<td>2 (28.5%)</td>
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<tr>
<td><strong>Highest academic degree</strong></td>
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<tr>
<td>• PhD or MD</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td>• Master’s degree</td>
<td>2 (28.5%)</td>
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<tr>
<td>• Bachelor’s degree</td>
<td>1 (14.3%)</td>
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<tr>
<td><strong>Academic and professional title</strong></td>
<td></td>
</tr>
<tr>
<td>• Full professor</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>• Associate chief physician or associate consultant</td>
<td>4 (57.1%)</td>
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<tr>
<td><strong>Years of professional experience</strong></td>
<td></td>
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<tr>
<td>• 5-10 years</td>
<td>1 (14.3%)</td>
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<tr>
<td>• 11-15 years</td>
<td>2 (28.5%)</td>
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<tr>
<td>• 16-20 years</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>• Over 20 years</td>
<td>3 (42.9%)</td>
</tr>
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Table 3 Content validity assessment of the true and placebo SAS protocol (number of experts=7)
<table>
<thead>
<tr>
<th>Item</th>
<th>Description of each item</th>
<th>True SAS intervention protocol</th>
<th>Placebo SAS intervention protocol</th>
<th>Scale level CVI</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>No. of experts rating as &quot;(4) very appropriate&quot;</td>
<td>No. of experts rating as &quot;(3) appropriate&quot;</td>
<td>No. of experts rating as (3) or (4)</td>
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<td>No. of experts rating as (3) or (4)</td>
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<td>1</td>
<td>Selection of acupoints formula</td>
<td>5</td>
<td>2</td>
<td>7</td>
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<td>2</td>
<td>SAS modality</td>
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<td>7</td>
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<td>3</td>
<td>SAS intensity and technique</td>
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<tr>
<td>4</td>
<td>SAS frequency and sessions</td>
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<td>5</td>
<td>SAS total duration</td>
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<td>Selection of acupoints formula</td>
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<td>5</td>
<td>SAS total duration</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
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</table>
4. Discussion

This study demonstrated how an evidence-based SAS intervention protocol for FSDSC management in BCS was developed and validated systematically following the MRC framework. In order to develop a research-informed, theory-driven, and practically feasible SAS intervention, an evidenced-based approach was adopted in this study with multiple supporting evidence from systematic reviews and clinical trials (the research evidence base), relevant modern medicine and TCM theories and SAS practical standards (knowledge and practice evidence base), and a content validity study (expert panel consensus). Methodological procedures that are presented in this study can provide important implications for future studies in the fields of integrative oncology and complementary therapies to develop evidence-based complex healthcare intervention that is tailored to specific health conditions.

Utilising appropriate methodological guidance can enhance the quality of research design, the likelihood of success of an intervention, and reduce ‘research waste’ [54,55]. In this study, the MRC framework, one of the most commonly used guidance for complex intervention development and evaluation, was utilised in this study. Following the MRC framework, a throughout identification of existing research evidence on SAS for FSDSC management was conducted prior to the intervention development to locate the best available research evidence base. Considering that high quality systematic reviews are viewed as ideal and reliable source of research evidence [55], findings from six well-conducted systematic reviews were utilised to build the research evidence base of this study for SAS intervention development. Learning the theories that underpin the proposed intervention can enhance the understanding of the mechanisms and actions within the causal chain and reduce the risk of developing a non-effective intervention [55]. In this study, relevant theories, including the inflammatory theory, the yin-yang theory, and the zang-fu organs and meridians theory, were adopted to clarify the causal mechanisms of using SAS for FSDSC alleviation in BCS. Systematic reviews provided key evidence regarding the identification of the most commonly used acupoint formula and SAS modality and dosage for the management of cancer-related fatigue, sleep disturbance and depression, with strong theoretical and practical rationale supported by relevant theories and practice standards. Developing the intervention through a combination of best available research evidence, theories and practice standards is a distinguished feature of this study to guarantee that the study procedures are research-informed, theory-driven and practically appropriate.

A “placebo control” is a commonly designed in acupoint stimulation study to distinguish the specific effects of acupoint stimulation from its non-specific effects (placebo effects) [56]. A placebo SAS method was developed in this study for use in the future clinical trial to help identify and size the specific effects of SAS for FSDSC management. Given that an inappropriate placebo method might result in some unwanted specific effects of acupoint stimulation and subsequently lead to a misjudgement of the causality between the intervention and outcomes [33], research evidence from large systematic reviews on placebo acupressure design were used in this study to guide the placebo intervention development. Non-acupoints located near the active acupoints used in the true SAS were identified as the placebo SAS
design, which could potentially facilitate a satisfactory blind design between the true and placebo interventions. Given that light stimulation of the non-acupoints may let some study participants (particularly those with previous experience of acupressure) identify the differences between the true and placebo interventions, the future clinical trial phase could consider only recruiting SAS-naïve BCS to minimize the risk of breaking the blind design.

Using a consensus method, for instance, involving experienced researchers and clinicians in the process of identifying and standardising the essential components of an intervention protocol, can contribute to more robust clinical integrity and acceptance of the intervention [57]. In this study, a panel of expert consisting of researchers and clinicians were involved to assess the proposed intervention protocol. Content validity of the true and placebo SAS interventions was determined as excellent, indicating that the SAS intervention protocol is theoretically and practically appropriate for FSDSC management in BCS. Although excellent agreement was obtained from the expert panel, suggestions were received to further refine the SAS protocol. One expert suggested that the sequence of acupoints should be specified and easy to be remembered by the study participants to ensure that all the acupoints are pressed without missing any. The research team therefore proposed the following sequence (from head to toe) for both the true and placebo interventions in accordance with clinical acupuncturist’ suggestion: 1) Baihui → 2) Yintang → 3) Neiguan → 4) Shenmen → 5) Hegu → 6) Zusanli → 7) Sanyinjiao → 8) Taixi → 9) Taichong → 10) Qihai → 11) Guanyuan.

Some limitations exist in this study. Although an in-depth understanding of the needs, preferences and opinions of lay experts (BCS in this study) is important for intervention development [55], cancer survivors were not included in the content validity study at this stage. Representativity of the expert panel might be another concern as purposive sampling method was used in the panel recruitment. The SAS protocol developed in this study can only be viewed as a preliminary stage of work, and future study phases, including a Phase II RCT, qualitative interviews, and fully-powered RCT, are necessary to further identify the feasibility, acceptability, and clinical utility of the SAS for the management of FSDSC in BCS.

**Conclusion**

This study detailed the methodological procedures in developing and validating an evidence-based SAS intervention for the FSDSC management in BCS by following the phase I of the MRC framework and comprehensively adopting best available evidence from systematic reviews, clinical trials, relevant theories, practical standards, and expert panel consensus to ensure that the SAS intervention is research-informed, theory-driven, and practically feasible. The feasibility, acceptability and clinical utility of the SAS intervention protocol for the FSDSC management in BCS will be further examined in a Phase II RCT.

**Abbreviations**

SAS: Somatic acupoint stimulation
Declarations

Funding

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Conflict of Interests

The authors declare that they have no conflict of interest.

Authors’ Contribution

Tan JY: study conception and design, data interpretation and checking, and manuscript revision; Wang T: study design, data collection, analysis and interpretation, and manuscript drafting and revision; Zhao I, Potolan MG, and Eliseeva S: study design and manuscript revision. All authors read and approved the final manuscript.

Ethics approval

Ethical approval of the project was granted by the Human Research Ethics Committee at Charles Darwin University in Australia (H19017).

Consent to participate

Informed consent was obtained from all the experts involved in the content validity study.

Consent for publication

N/A.

Acknowledgments

We would like to thank the expert panel members who participated in the content validation study.
Disclosures (Conflict of Interest)

None declared.

References


Figures

Development of the SAS intervention protocol

Identification of current evidence base
- Systematic review 1: current evidence on SAS for fatigue management
- Systematic review 2: current evidence on SAS for sleep disturbance management
- Systematic review 3: current evidence on SAS for depression management
- Systematic review 4: current evidence on sham SAS design

Identification of theories and practice standards
- Neurophysiological theory: inflammatory theory
- TCM theories: yin-yang theory and zang-fu organs and meridians theory
- Practice standards of SAS

Validation of the SAS protocol
- Content validation of the SAS intervention protocol via a panel of experts specialized in oncology, Chinese medicine and/or acupoints stimulation

Research evidence to support:
- Commonly used acupoints formula
- Appropriate SAS modality
- Appropriate SAS dosage
- Appropriate sham SAS design

Theories and practice standards to support:
- Potential mechanism of the SAS intervention
- Appropriate acupoints formula
- Appropriate SAS modality
- Appropriate SAS intensity and technique
- Appropriate SAS dosage (frequency, sessions and total duration)

Content validity study to:
- Examine the content validity of the SAS intervention protocol using the CVI
- Collect suggestions and comments from the panel to further refine the SAS protocol

The preliminary SAS intervention protocol

Figure 1

Overview of the study process

**SAS**: Somatic acupoints stimulation; **CVI**: Content validity index

Supplementary Files

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- 2.Supplementaryfile.docx