Study Title: Patient-centred self-administered acupressure for Chinese advanced cancer patients experiencing fatigue and co-occurring symptoms: A pilot randomised controlled trial

Authors:

Denise Shuk Ting Cheung1, denisest@hku.hk;

Wing Fai Yeung2, jerry-wf.yeung@polyu.edu.hk;

Pui Hing Chau1, phpchau@hku.hk;

Tai Chung Lam3, lamtc03@hku.hk;

Mingxiao Yang4, mxyang@hku.hk;

Kithelia Lai5, kithelialai@gmail.com;

Chun Yat Ip5, ipcy1@ha.org.hk;

Lixing Lao4, lxlao1@hku.hk;

Chia-Chin Lin1, cclin@hku.hk

1School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Hong Kong, China

2School of Nursing, The Hong Kong Polytechnic University, Hung Hom, Kowloon

3Departtment of Clinical Oncology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 1/F, Professorial Block, Queen Mary Hospital, Pokfulam, Hong Kong, China

4School of Chinese Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 10 Sassoon Road, Pokfulam, Hong Kong

5Departtment of Clinical Oncology, Queen Mary Hospital, 1/F, Professorial Block, Queen Mary Hospital, Pokfulam, Hong Kong, China

Correspondence:

Prof Chia-Chin Lin

School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 4/F William MW Mong Block Building, 21 Sassoon Rd, Pokfulam, Hong Kong. (Email: cclin@hku.hk; Phone: +852 3917 6633)

Ethical approval

Institutional Review Board of The University of Hong Kong / Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB: UW 18-381)

Abstract

Objectives

To evaluate the feasibility and potential effects of patient-centred self-administered acupressure for alleviating fatigue and co-occurring symptoms among Chinese advanced cancer patients receiving treatment.

Methods

Thirty advanced cancer patients who screened positive for moderate/severe fatigue with symptoms of insomnia and/or pain were recruited from a hospital in Hong Kong. They were randomly assigned (1:1) to receive a 4-week patient-centred self-administered acupressure intervention or health education. Fatigue (primary outcome) and secondary outcomes (sleep quality, pain, fatigue-sleep disturbance-pain symptom cluster severity, anxiety, depression, and quality of life) were measured by questionnaires and actigraphy.

Results

Twenty-four participants (80%) completed the study. Adherence to self-administered acupressure practice was satisfactory, with all retained participants attending all sessions and 90.9% practising acupressure daily. All completers rated the class as very enjoyable or quite enjoyable. Fatigue, pain, symptom cluster severity, anxiety, depression, and quality of life appeared to improve from baseline to post-intervention in the intervention group. Among these outcomes, only the between-group difference in anxiety post-intervention was significant. The group × time interaction effect was nonsignificant for all outcomes.

Conclusions

Patient-centred self-administered acupressure appears to be feasible and acceptable among advanced cancer patients. A fully powered trial is warranted to confirm the intervention effect.

ClinicalTrials.gov Identifier: NCT03610243

Keywords: Acupressure, advanced cancer, fatigue, traditional Chinese medicine, insomnia, pain

Introduction

Persistent fatigue is the most prevalent and, for some, the most distressing symptom of cancer (Berger et al., 2015). It is a nearly universal symptom in advanced cancer sufferers, affecting up to 97% of such patients (Tsai et al., 2012). Although its exact aetiology remains unclear, contributory factors include tumours, treatment and comorbidities. The coexistence of fatigue with other symptoms (such as sleep disturbance, pain and psychological distress) as a symptom cluster is frequently reported in the literature and it greatly compromises the health-related quality of life (HQOL) in advanced cancer patients (Dong et al., 2016; Rodrigues, Trufelli, Fonseca, de Paula, & Giglio, 2016). Despite the significant impact on patients' lives, fatigue has been largely under-recognised and poorly managed by healthcare professionals (Bower, 2014).

In patients with advanced-stage cancer, no specific drug can be recommended for treating fatigue according to a Cochrane review (Mücke et al., 2016). Nonpharmacologic approaches have been proposed as useful alternatives (Hilfiker et al., 2018; Mustian et al., 2017), with examples being physical exercise (Oldervoll et al., 2011) and cognitive-behavioural strategies (Kwekkeboom et al., 2012). Compared with pharmacologic strategies, nonpharmacological treatments have fewer adverse effects that contribute to other symptoms, and their mechanisms of action may be more broadly beneficial across symptoms (Kwekkeboom, 2016). However, they may be limited by challenges to implementation. For example, fatigue is one of the most commonly reported barriers to exercise (Blaney et al., 2010; Clifford et al., 2018), while behavioural treatments are hindered by poor availability of mental health professionals and high costs (Hilfiker et al., 2018). Therefore, a simple, inexpensive, self-care strategy is needed for treating fatigue in advanced cancer patients receiving treatment.

Acupressure is a non-invasive technique based on the meridian theory of traditional Chinese medicine (TCM) (Yeung et al., 2012a). Meridians, which are channels in the network of energy pathways throughout the body, regulate the flow of *qi* (vital energy). Applying pressure to acupoints on the skin surface stimulates the meridians, resulting in the opening of the channels and the balancing of energy, thus restoring health. Acupressure can be self-administered, meaning that recipients can perform it themselves. Specifically, among cancer patients, self-administered acupressure has shown promise for reducing fatigue in treatment-free cancer survivors (Molassiotis, Sylt, & Diggins, 2007; Zick et al., 2016). However, whether self-administered acupressure is feasible and effective for fatigue management in incurable cancer patients receiving treatment is not known.

While previous acupressure studies used a fixed acupoints protocol for simplicity (Molassiotis et al., 2007; Zick et al., 2016), our intervention is the first to provide an individualised protocol for each patient based on a pool of preselected acupoints. Since patients may have diverse symptoms and varied sensitivity to acupoint stimulation, it is important to provide individualised recommendations regarding acupoint selection for self-administered acupressure. Such an individualised approach in acupoint selection is

consistent with the emphasis of patient-centred interventions, which are interventions altered to address the individual needs of care recipients (Lauver et al., 2002). Although individualised protocols are increasingly used in acupuncture trials (Conboy et al., 2016; He et al., 2019; Landgren, Tiberg, & Hallström, 2015), they have not been tested in any self-administered acupressure studies.

The specific aims of this study were (a) to test the feasibility and acceptability of a patient-centred self-administered acupressure intervention among Chinese advanced cancer patients receiving cancer treatment and (b) to evaluate the potential effects of self-acupressure for reducing fatigue (primary outcome) and related symptoms (secondary outcomes of insomnia, pain, psychological distress, HQOL and fatigue-sleep disturbance-pain [FSDP] symptom cluster severity) in comparison with health education. Although this exploratory pilot study did not involve formal statistical significance testing, the results and participants' feedback from this pilot study will inform the design and sample size calculation for future fully powered trials. Symptom improvement may lead to an improvement in patients' functioning and quality of life, which in turn may reduce health service utilisation and healthcare costs.

Methods

Trial Design, Setting and Participants

A pilot randomised controlled trial (RCT) comparing self-administered acupressure with health education was conducted between August 2018 and May 2019 in Hong Kong. Inclusion criteria were Chinese ethnicity, 18 years of age or older, ability to communicate in Cantonese or Putonghua, advanced-stage cancer diagnosis (i.e., the most prevalent cancer types in Hong Kong, including colorectum–Stage IV; lung–Stage IIIB or IV non-small cell or extensive small cell; breast–Stage IV; prostate–Stage IV; or liver–Stage IV), an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and experience of fatigue (rated ≥ 4 on the 'fatigue worst' item of the Brief Fatigue Inventory [BFI]) AND sleep disturbance or pain, or both, in the past week (severity rated ≥ 3 on a 0–10 numeric rating scale). Individuals were excluded if they were receiving in-patient hospice care, were not receiving cancer treatment, were taking any medications for insomnia or depression, had psychiatric or serious medical disorders or had received acupressure or acupuncture in the previous 3 months.

The participants were recruited from the oncology department of a regional, public-funded hospital in Hong Kong. All participants provided written informed consent. A sample size of at least 12 per group in a pilot RCT has been recommended by previous literature (Julious, 2005). This should provide sufficient methodological experience and estimation of effect size for subsequent fully powered studies. Assuming a dropout rate of 20%, at least 15 subjects per group were needed.

Randomisation, Allocation Concealment and Blinding

Participants were randomly assigned to either the intervention group or the health education group at a 1:1 ratio using block randomisation with a random block length. A randomiser unconnected to the study generated the randomisation list by computer and placed the assignment results in separate, sequentially numbered, sealed, opaque envelopes. The randomiser kept a secure copy of the randomisation codes, and the envelopes containing participants' group assignment were centrally controlled by a staff member not involved in recruitment. Neither the research assistant conducting recruitment nor the participants knew the group assignments until the envelopes were opened. Outcome assessors and research assistants who entered and analysed data were blinded.

Intervention and Health Education Conditions

Intervention group

The self-administered acupressure intervention was developed by expert consensus based on previous literature relating to fatigue and related symptom management (Molassiotis et al., 2007; Yeung et al., 2012b; Zhang, Chen, Yip, Ng, & Wong, 2010; Zick et al., 2016). The team has extensive experience in designing acupressure protocols for diverse populations (D. S. T. Cheung et al., 2020; Yeung et al., 2018). The protocol for this study covered four preselected acupoints to which pressure should be applied by all patients and a list of additional acupoints from which trainers could recommend two based on patients' symptoms, sensitivity and preferences. In this way, each patient received an individualised protocol (four preselected and two self-selected acupoints as recommended by trainers). The protocol is summarised in Appendix 1, while the locations of the acupoints are in Figure 1.

The intervention lasted 4 weeks, consisting of (a) training: two 2-hour training sessions in self-administered acupressure in 1 week (4 hours), (b) follow-up: three 1-hour weekly follow-up visits for reinforcing practice over 3 weeks (3 hours) and (c) self-practice: participants were instructed to perform 15 minutes of self-administered acupressure twice a day after completing the two training sessions (once in the morning and once in the afternoon or evening; 10.5 hours). The training was delivered by a senior-year TCM student and a nursing student in the patient's home or at the university, depending on his or her preference. The content of the training sessions was standardised, as indicated in Appendix 2. Participants had to log the frequency of self-practice in a diary throughout the study period.

Several measures were adopted to standardise delivery and replicability. First, a total of six trainers were trained and certified by two licensed TCM practitioners. Second, participant training made use of a standardised teaching aid comprising a resource book detailing relevant theories and the acupressure protocol, as well as standardised learning materials provided for participants (i.e., a booklet and a poster). Third, all patients were assessed by the trainers post-intervention regarding the number of acupoints correctly

located and proper technique demonstration with the use of a competency checklist (Appendix 3) to ensure successful standardisation of the intervention.

Health education group

The health education group received the usual care, and it was contacted in the third week to attend a health talk unrelated to symptom management. After the study, the participants were offered the same intervention as the intervention group.

Procedures

Data were collected for all participants using the same procedures at three time-points: baseline, post-intervention (after 4 weeks) and follow-up (after 8 weeks, i.e., 4 weeks after intervention completion). The primary outcome measure was fatigue. Secondary outcome measures included sleep disturbance, pain, psychological distress, HQOL, FSDP symptom cluster severity and actigraphic parameters to assess objective sleep quality. Questionnaires were administered face to face by a trained research assistant who was blinded to participants' group allocation. The data collection points are in Figure 2.

Feasibility- and Acceptability-Related Outcomes

Rates of eligibility, recruitment, adherence and retention were calculated as stated in Appendix 4. Adverse events were recorded by the trainers (if any) as 'related' or 'unrelated' to the study. To explore participants' experience of and satisfaction with the intervention and study methods, a satisfaction questionnaire composing of 13 questions was administered at the end of the acupressure intervention. The health education group participants were also invited to complete the questionnaire after they received the acupressure intervention during the post-study period.

Effect-Related Outcomes

The Chinese BFI (primary outcome measure; nine items; score range: 0-10) was used to assess fatigue levels. It consists of two subscales: fatigue severity (3 items) and interference (6 items). The BFI has demonstrated satisfactory internal consistency and validity in Chinese patients (Wang et al., 2004).

The Chinese Pittsburgh Sleep Quality Index (PSQI; 19 items; score range: 0-21) was used to assess sleep disturbance levels. The PSQI has been validated and it has demonstrated satisfactory internal consistency and test-retest reliability in Chinese populations (Tzeng, Fu, & Lin, 2012).

The Chinese Brief Pain Inventory (BPI) pain severity subscale (4 items; score range: 0-10) was used to assess pain intensity. The BPI has demonstrated internal consistency, as well as construct, convergent and known-group validity for Chinese populations (Wang, Mendoza, Gao, & Cleeland, 1996).

The Hospital Anxiety and Depression Scale (HADS; 14 items; score range: 0-21) was used to measure the severity of psychological distress. It consists of two 7-item subscales: anxiety and depression. The HADS has shown satisfactory psychometric properties including internal consistency, concurrent validity and construct validity in Chinese advanced cancer patients (Li et al., 2016).

The Functional Assessment of Cancer Therapy–General (FACT-G; 27 items; score range: 0-108) (Yu et al., 2000) was used to assess HQOL. It consists of four subscales: physical, emotional, social/family, and functional well-being. The FACT-G has been validated in Chinese populations with good reliability, convergent validity and divergent validity.

Actigraphy served as an objective measure of sleep quality (Yennurajalingam et al., 2016). Participants were asked to wear the ActiGraph for three separate 72-hour periods at baseline, post-intervention, and follow-up. Parameters of the sleep-wake patterns (including total sleep time and sleep efficiency) were analysed by the accompanying software.

A demographic questionnaire was used at baseline to collect information on participants' background characteristics and disease information (e.g., cancer diagnosis, ECOG PS and cancer treatment). Information was retrieved from medical records if necessary.

Data Analysis

Analysis was performed by an independent researcher who was unaware of the group allocation using an intention-to-treat approach with the Statistical Package for the Social Sciences version 25.0 (IBM Corp., Armonk, NY, United States). The background characteristics for the intervention and the health education groups were assessed by a chi-square test and a *t* test for categorical and continuous data, respectively. Feasibility-related outcomes (rates of recruitment, retention and adherence) were presented as descriptive statistics.

For effect-related outcomes, an intention-to-treat approach was used. Inferential analysis was performed using the mixed-effects model because it can accommodate missing data without manual imputation, thereby providing a natural way to deal with missing values or dropouts (Chakraborty & Gu, 2009). The mean scores of BFI, PSQI, BPI, HADS, FACT-G, and actigraphic parameters were reported at each time point, accompanied with 95% CI. To quantify FSDP symptom cluster severity, the scores of the BFI and BPI severity subscales and the item on overall sleep quality in the PSQI were averaged. In addition, between-group effect sizes were computed by dividing the difference between group means by the pooled standard deviation. Although pilot studies should primarily focus on descriptive statistics (Lee, Whitehead, Jacques, & Julious, 2014), statistical significance was also tested using the mixed-effects model for exploratory purposes.

Results

Baseline Characteristics

Table 1 provides information on the demographics of the participants (n = 30). Most participants were female (80%) and suffered from lung cancer (40%). The intervention group participants were aged 61.80 years (SD = 9.92) and those in the health education group were aged 58.93 years (SD = 11.11) on average. The average number of months since diagnosis was 45.71 (SD = 46.70) and 32.43 (SD = 19.23) among participants in the intervention and health education groups, respectively. The types of cancer treatment patients were receiving included chemotherapy, targeted therapy, immunotherapy, radiotherapy and/or hormonal therapy. At baseline, there were no significant differences in the participants' background characteristics or the outcome measures between the two groups.

Feasibility- and Acceptability-Related Outcomes

Recruitment

Figure 2 shows the recruitment flow. A total of 820 cancer patients were assessed for eligibility in six clinic sessions, and 650 individuals did not meet the inclusion criteria. Among the 170 potentially eligible individuals, 103 were contacted, 16 were further confirmed as ineligible and 30 agreed to participate. These figures indicate an eligibility rate of 11.5% and a recruitment rate of 29.13% of eligible patients. Fifteen patients were randomised to intervention and 15 to health education.

Retention rate, participant adherence and intervention acceptability

Six participants withdrew from the trial due to deteriorated conditions unrelated to the study. The retention rate was thus 80% of those randomised (11 intervention participants and 13 health education participants). The remaining 11 intervention group participants who completed the study attended all the training and follow-up sessions. All 11 participants returned self-practice diaries, and 10 participants practised at least once daily during the intervention period, indicating an adherence rate of 90.9%. Competency assessment scores ranged from 38 to 44, with an average of 42.90 (SD = 2.03) out of 44. A total of 19 intervention and health education group patients returned the post-intervention satisfaction questionnaire. The results are in Appendix 5. They rated the class as either very enjoyable (63.16%) or quite enjoyable (36.84%), and none was unsatisfied. Positive ratings were consistently given for items on satisfaction with study logistics. No adverse events were reported. All participants completed all outcome measurement items, including the use of wearable activity monitors, except those who withdrew from the study.

Effect-Related Outcomes

Primary outcome

Table 2 presents the findings for the primary and secondary outcomes in the intervention and health education groups at all time points.

In the intervention group, the BFI global scores decreased after 4 weeks (mean difference, MD = -0.81, 95% CI, -2.41 to 0.79). At 8-week follow-up, although the BFI global scores slightly rebounded, there was an overall improvement relative to the baseline values (MD = -0.58, 95% CI, -2.81 to 1.65). In the health education group, a similar pattern of change in BFI global scores, but of smaller magnitude, was observed after 4 weeks (MD = -0.32, 95% CI, -1.84 to 1.21) and 8 weeks (MD = -0.01, 95% CI, -2.12 to 2.10). The change in BFI severity and BFI interference scores followed the same trend as the BFI global scores in both groups. However, the between-group difference in BFI global, severity, and interference scores at Week 4 and Week 8 did not reach statistical significance.

Secondary outcomes

After 4 weeks, improvement was observed in the intervention group in BPI severity (MD = -0.35, 95% CI, -1.89 to 1.19), HADS anxiety (MD = -1.98, 95% CI, -4.57 to 0.61), HADS depressive scores (MD = -0.72, 95% CI, -2.53 to 1.09), FACT-G (MD = 3.98, 95% CI, -2.04 to 10.01) and FSDP symptom cluster severity (MD = -0.87, 95% CI, -1.85 to 0.12). In the health education group, there was a slight improvement for PSQI (MD = -0.75, 95% CI, -2.47 to 0.98) and FSDP symptom cluster severity (MD = -0.45, 95% CI, -1.39 to 0.49). However, only the between-group difference in HADS anxiety subscale and the PSQI score were statistically significant (between-group MD: anxiety = -3.39, 95% CI, -6.59 to -0.19; PSQI = 2.66, 95% CI, 0.24 to 5.09).

After 8 weeks, the HADS anxiety and depressive scores in the intervention group continued to decrease (anxiety: MD = -2.15, 95% CI, -5.03 to 0.74; depression: MD = -1.48, 95% CI, -3.86 to 0.90), while the other scores either rebounded or remained similar. Similarly, the health education group's improvement in PSQI and FSDP symptom cluster severity diminished after 8 weeks. At this point, no secondary outcomes showed significant between-group differences.

Regarding the change in between-group difference over time, group × time interaction effect was not significant for the primary and secondary outcomes. We repeated the analyses controlling for potential confounders (i.e., number of months since cancer diagnosis and anaemia). The results did not alter, except that the between-group difference in the PSQI scores at Week 4 became statistically nonsignificant (between-group MD = 2.404, 95% CI, -0.26 to 5.07) and that in the HADS anxiety subscale at Week 8 became statistically significant (between-group MD = -3.54, 95% CI, -6.37 to -0.71) in the adjusted model.

Actigraphic parameters

Table 3 shows the findings for the actigraphic parameters. After 4 weeks, total sleep time increased in both intervention (MD = 37.33, 95% CI, -35.52 to 111.18) and health education groups (MD = 19.66, 95% CI, -49.04 to 88.36), but it decreased after 8 weeks for both groups. A slight improvement in sleep efficiency after 4 weeks was only observed in the intervention group, and it had diminished after 8 weeks.

Discussion

Principal Findings and Comparison with Previous Literature

This pilot trial has shown that training Chinese advanced cancer patients receiving cancer treatment to self-administer acupressure using a patient-centred approach by providing individualised protocols is feasible and acceptable. The trial has also indicated improvement for fatigue, pain, psychological distress, and HQOL post-intervention, although statistical significance was not reached, probably due to the small sample size. Estimates of effect sizes have been generated for future fully powered studies based on the current study. The rebound in fatigue and pain at follow-up could be because the intervention did not include adequate strategies focused on long-term maintenance of self-practice. Developing a mobile application consisting of automatic reminders and video demonstrations for technique review may aid in retaining self-practice and maintaining long-term effects. If the intervention proves effective, symptom management will be simplified by offering a single intervention for multiple co-occurring symptoms. Also, the intervention will serve as a significant addition to fatigue management targeting advanced cancer patients. However, an RCT with a large sample size is needed to confirm the effect.

Approximately one third of those approached were successfully recruited, which is satisfactory, particularly given that our sample was advanced cancer patients with high symptom burden and a high chance of deteriorating conditions (LeBlanc, Lodato, Currow, & Abernethy, 2013). The recruitment rate (29.13%) is comparable to that of previous psychosocial RCTs, which also targeted advanced cancer patients and included a similar number of sessions to our study (~25.1%-39.8%) (E. O. Cheung et al., 2017; Greer et al., 2012; Lo et al., 2019). In addition, the retention rate of 80% is relatively high compared to the completion rate reported by a systematic review examining psychosocial interventions for advanced cancer patients (~70-75%) (Teo, Krishnan, & Lee, 2019). Concerning intervention adherence, the retained participants attended all the training and follow-up sessions, they passed the competency check, and more than 90% of participants performed self-practice at least once daily during the intervention period. All these factors indicated satisfactory acceptability and feasibility among the advanced cancer patients of learning and performing self-administered acupressure. In addition, the high rates of completion of outcome measurement provide reassurance that the selected outcome measures were appropriate and broadly acceptable to patients.

To our knowledge, the current study is the first attempt to adopt a patient-centred approach for a self-administered acupressure intervention by providing patients with individualised protocols and to test it with a rigorous study design to enhance intervention fidelity. There is a growing movement to engage patients and to consider their individual needs in research to improve the quality of care (Fergusson et al., 2018). Taking this into account, we provided individualised recommendations for patients regarding acupoint selection, rather than using a fixed acupoint protocol as in previous studies. This personalised approach is consistent with advanced cancer patients' need for an intervention that is flexible to accommodate symptom variations (Mosher, Ott, Hanna, Jalal, & Champion, 2017), and this may have contributed to the high adherence rate. Also, the intervention is rooted in TCM; hence, it is culturally specific to Chinese patients and it may increase the salience and sustainability of the intervention.

Research Implications

A fully powered RCT is warranted. To improve recruitment further, effective strategies for increasing recruitment from the literature can be adopted, such as reminders to those who expressed interest on site but needed time to consider and including a financial incentive for completion of the study (Treweek et al., 2013). Future research can compare the characteristics of eligible consenting and nonconsenting patients to assess whether participants are representative of the target population. To explore possible explanations for sustained/diminished intervention effect at follow-up, a competency check can be conducted at follow-up to assess whether participants' accuracy of acupressure technique sustains. In addition, patients' preferences regarding acupoint selection should be recorded with reasons by the trainers to inform future protocol design.

Clinical Implications

The present pilot study informs the design of a fully powered RCT, which will help health-care workers in clinical settings to inform their advanced cancer patients of an evidence-based intervention that can alleviate fatigue and related symptoms. In addition, the successful training of healthcare students to act as trainers in the trial will demonstrate the potential for training health professionals to deliver self-administered acupressure training to patients. If proven effective, the protocol can be incorporated into existing education programs for cancer patients with little healthcare professional or patient burden.

Limitations

First, the study lacks statistical power, as it is a pilot study. Therefore, emphasis was placed on descriptive statistics instead of statistical significance (Lee et al., 2014). Second, the social interactions during intervention training might have served as important elements of the intervention and resulted in attention bias, which may have influenced the results. A third limitation concerns the generalisability of the findings. The study sample was comprised of Chinese patients only. Thus, whether these findings could be replicated with other ethnic groups is not known. Fourth, the patients who completed

the satisfaction surveys are likely those who liked the intervention; therefore, the acceptability may be positively biased. Finally, given that the literature on Chinese cancer patients has reported comparable fatigue severity among the major disease groups (Wang et al., 2004), we chose to adopt an inclusive approach to targeting advanced-stage cancer patients. Inclusion of all cancer diagnoses may have resulted in an increased heterogeneity and confounding. Therefore, such a potential confounding effect should be considered in data analysis of the future adequately powered RCT.

Conclusions

The patient-centred, self-administered acupressure appeared to be feasible, acceptable, safe and easy to learn for Chinese advanced cancer patients receiving cancer treatment. Although fatigue symptoms showed a decreasing trend from baseline to post-intervention in the intervention group, groups were similar in fatigue symptoms post-intervention. Confirmation of intervention effect in a future fully powered RCT is required.

Contribution of Paper

Study concept and design: Cheung, Yeung, Chau, Lam, Yang, Lai, Lao, Lin

Acquisition of data: Cheung, Lam, Lai, Ip

Analysis and interpretation of data: Cheung, Yeung, Chau

Drafting of the manuscript: Cheung, Yeung

Critical revision of the manuscript for important intellectual content: Cheung, Yeung, Chau, Lam, Yang, Lai, Ip, Lao, Lin,

Administrative, technical, or material support: Cheung, Lin

Study supervision: Cheung, Yeung, Yang

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Table 1. Baseline Characteristics

	Group, Number (%)		
Background Characteristics	**Intervention (*n* = 15)**	**Health education (*n* = 15)**	***P* value**
Age, mean ± SD, years	61.8 ± 9.92	58.93 ± 11.11	0.46
Female	12 (80.0%)	12 (80.0%)	1.00
Education			0.67
Primary or below	4 (26.7%)	3 (20.0%)	
Secondary or above	11 (73.3%)	12 (80.0%)	
Having a caregiver	11 (73.3%)	10 (66.7%)	0.69
Marital status			0.67
Single/divorced	3 (20.0%)	4 (26.7%)	
Married/cohabiting	12 (80.0%)	11 (73.3%)	
ECOG PS = 0	2 (13.3%)	2 (13.3%)	0.94
Experiencing financial hardship	4 (26.7%)	4 (26.7%)	1.00
Metastatic	14 (93.3%)	12 (80.0%)	0.28
Site of cancer			0.60
Colorectal	4 (26.7%)	3 (20.0%)	
Lung	5 (33.3%)	7 (46.7%)	
Breast	6 (40.0%)	4 (26.7%)	
Prostate	0 (0%)	1 (6.7%)	
Number of months since cancer diagnosis ± SD	45.71 ± 46.70	32.43 ± 19.23	0.34
Haemoglobin level below 11.5g/dL	5 (35.7%)	1 (7.1%)	0.07
Receiving chemotherapy[a]	7 (46.7%)	4 (26.7%)	0.26

[a]Patients were either receiving chemotherapy alone or in conjunction with other therapies.

[b]*P* value obtained by chi-square test or *t* test.

Note: SD is standard deviation.

Table 2: Primary and secondary outcomes

	Intervention (*n* = 15)		Control (*n* = 15)		Between-group difference at each time point	Effect size[g] (95% CI)	Group × time interaction effect *P* value
	Mean (95% CI)	Within-group change from baseline (95% CI)	Mean (95% CI)	Within-group change from baseline (95% CI)	Mean (95% CI)		
[a]BFI Global							0.83
Baseline	3.80 (2.75, 4.85)	/	4.13 (3.08, 5.18)	/	-0.33 (-1.82, 1.15)		
Post-intervention	2.99 (1.90, 4.08)	-0.81 (-2.41, 0.79)	3.82 (2.80, 4.83)	-0.32 (-1.84, 1.21)	-0.83 (-2.32, 0.66)	-0.41 (-1.13, 0.32)	
Follow-up	3.22 (1.67, 5.55)	-0.58 (-2.81, 1.65)	4.12 (2.69, 5.55)	-0.01 (-2.12, 2.10)	-0.90 (-3.01, 1.21)	-0.32 (-1.03, 0.41)	
[a]BFI Severity							0.75
Baseline	5.13 (4.26, 6.01)	/	5.16 (3.39, 5.59)	/	-0.02 (-1.26, 1.22)		
Post-intervention	3.88 (2.71, 5.05)	-1.25 (-2.75, 0.25)	4.49 (3.39, 5.59)	-0.67 (-2.08, 0.74)	-0.61 (-2.21, 1.00)	-0.28 (-1.00, 0.44)	
Follow-up	4.33 (2.69, 5.97)	-0.80 (-3.10, 1.49)	4.63 (3.11, 6.14)	-0.53 (-2.69, 1.63)	-0.30 (-2.53, 1.94)	-0.10 (-0.82, 0.62)	

[a]BFI Interference							0.81
Baseline	3.13 (1.90, 4.37)	/	3.62 (2.39, 4.86)	/	-0.49 (-2.23, 1.26)		
Post-intervention	2.54 (1.32, 3.75)	-0.60 (-2.46, 1.27)	3.48 (2.35, 4.61)	-0.60 (-1.93, 1.65)	-0.94 (-2.60, 0.72)	-0.41 (-1.14, 0.31)	
Follow-up	2.64 (1.03, 4.26)	-0.49 (-2.77, 2.44)	3.90 (2.41, 5.40)	0.28 (-1.87, 2.44)	-1.26 (-3.46, 0.94)	-0.42 (-1.15, 0.31)	
[b]PSQI							0.06
Baseline	7.20 (5.75, 8.65)	/	5.73 (4.28, 7.19)	/	1.47 (-0.59, 3.52)		
Post-intervention	7.65 (5.87, 9.43)	0.45 (-1.47, 2.37)	4.99 (4.28, 7.19)	-0.75 (-2.47, 0.98)	2.66 (0.24,5.09)	0.46 (-0.27, 1.18)	
Follow-up	6.22 (4.75, 7.68)	-0.99 (-2.57, 0.60)	5.53 (4.11, 6.95)	-0.20 (-1.71, 1.31)	0.68 (-1.36, 2.73)	0.25 (-0.47, 0.97)	
[c]BPI Severity							0.84
Baseline	2.45 (1.39, 3.51)	/	2.50 (1.44, 3.56)	/	-0.05 (-1.55,1.45)		
Post-intervention	2.10 (1.06, 3.14)	-0.35 (-1.89, 1.19)	2.52 (1.54, 3.49)	0.02 (-1.49, 1.46)	-0.41 (-1.84, 1.02)	-0.22 (-0.93, 0.50)	
Follow-up	2.61 (1.37, 3.85)	0.16 (-1.52, 1.83)	3.18 (2.02, 4.34)	0.68 (-0.90, 2.26)	-0.57 (-2.27,1.12)	-0.25 (-0.97, 0.47)	

[d]HADS Anxiety							0.11
Baseline	5.67 (4.08, 7.25)	/	6.07 (4.48, 7.65)	/	-0.40 (-2.65, 1.85)		
Post-intervention	3.69 (1.36, 6.01)	-1.98 (-4.57, 0.61)	7.08 (4.88, 9.28)	1.01 (-1.40, 3.43)	-3.39 (-6.59, -0.19)	-0.78 (-1.52, -0.04)	
Follow-up	3.52 (1.43, 5.62)	-2.15 (-5.03, 0.74)	5.91 (3.96, 7.85)	-0.16 (-2.89, 2.57)	-2.39 (-5.24, 0.47)	-0.62 (-1.35, 0.11)	
[d]HADS Depression							0.10
Baseline	6.53 (4.54, 8.53)	/	5.40 (3.41, 7.39)	/	1.13 (-1.68, 3.95)		
Post-intervention	5.81 (3.76, 7.86)	-0.72 (-2.53, 1.09)	5.42 (3.44, 7.41)	0.02 (-1.67, 1.72)	0.39 (-2.47, 3.24)	0.10 (-0.62, 0.82)	
Follow-up	5.05 (2.70, 7.41)	-1.48 (-3.86, 0.90)	6.63 (4.38, 8.89)	1.23 (-0.98, 3.44)	-1.58 (-4.84, 1.68)	-0.36 (-1.08, 0.37)	
[e]FACT-G							0.06
Baseline	75.27 (68.96, 81.57)	/	79.20 (72.90, 85.51)	/	-3.93 (-12.85, 4.98)		
Post-intervention	79.25 (72.46, 86.03)	3.98 (-2.04, 10.00)	75.02 (68.44, 81.60)	-4.18 (-9.80, 1.43)	4.23 (-5.22, 13.69)	0.33 (-0.39, 0.25)	
Follow-up	79.92 (70.92, 88.92)	4.65 (-5.39, 14.69)	78.36 (69.90, 86.81)	-0.84 (-10.08, 8.39)	1.56 (-10.78, 13.91)	0.09 (-0.62, 0.81)	

[f]FSDP Symptom Cluster Severity							0.63
Baseline	4.30 (3.54, 5.07)	/	4.03 (3.27, 4.80)	/	0.27 (-0.81, 1.35)		
Post-intervention	3.44 (2.68, 4.20)	-0.87 (-1.85, 0.12)	3.58 (2.86, 4.30)	-0.45 (-1.39, 0.49)	-0.14 (-1.19, 0.90)	-0.10 (-0.82, 0.62)	
Follow-up	3.48 (2.68, 4.20)	-0.83 (-2.22, 0.57)	3.89 (2.91, 4.88)	-0.14 (-1.45, 1.17)	-0.41 (-1.86, 1.03)	-0.21 (-0.93, 0.51)	

[a]The score range is 0 to 10, higher scores represent higher fatigue overall levels/severity/interference; [b]The score range is 0 to 21, higher scores represent more severe sleep disturbance; [c]The score range is 0 to 10, higher scores represent higher pain severity; [d]The score range is 0 to 21, higher scores represent more severe anxiety/depressive symptoms; [e]The score range is 0 to 108, higher scores represent higher health-related quality of life; [f] The score range is 0 to 10, higher scores represent higher FDSP symptom cluster severity; [g]computed by dividing the difference between group means by the pooled standard deviation.

Notes. BFI: Brief Fatigue Inventory; PSQI: Pittsburgh Sleep Quality Index; BPI: Brief Pain Inventory; HADS: Hospital Anxiety and Depression Scale; FACT-G: Functional Assessment of Cancer Therapy – General; FSDP: fatigue-sleep disturbance pain.

Table 3: Actigraphic parameters

	Intervention (*n* = 15)		Control (*n* = 15)		Between-group difference at each time point	Effect size[a] (95% CI)	Group × time interaction effect *P* value
	Mean (95% CI)	Within-group change from baseline (95% CI)	Mean (95% CI)	Within-group change from baseline (95% CI)	Mean (95% CI)		
Total sleep time, min							0.70
Baseline	266.85 (225.89, 307.82)	/	280.29 (239.33, 321.25)	/	-13.44 (-71.36, 44.50)		
Post-intervention	304.18 (248.76, 359.61)	37.33 (-35.52, 110.18)	299.95 (248.18, 351.71)	19.66 (-49.04, 88.36)	4.24 (-71.59, 80.07)	0.04 (-0.68, 0.76)	
Follow-up	271.60 (227.00, 316.19)	4.74 (-47.31, 56.80)	261.73 (218.44, 305.02)	-18.56 (-68.85, 31.74)	9.863 (-52.28, 72.01)	0.12 (-0.60, 0.83)	
Sleep efficiency, %							0.16
Baseline	91.20 (89.30, 93.10)	/	92.09 (90.19, 93.98)	/	-0.88 (-3.57, 1.80)		
Post-intervention	93.38 (91.43, 95.33)	2.18 (-0.35, 4.71)	91.54 (89.70, 93.38)	-0.55 (-2.95, 1.86)	1.84 (-.84, 4.52)	0.50 (-0.22, 1.23)	
Follow-up	91.96 (89.76, 94.16)	0.76 (-2.25, 3.77)	90.74 (88.63, 92.84)	-1.35 (-4.26, 1.56)	1.22 (-1.82, 4.27)	0.21 (-0.51, 0.93)	

[a]computed by dividing the difference between group means by the pooled standard deviation.

Figure legends:

Figure 1. Location of acupoints

Figure 2. Study flow

Appendix 1. Protocol of the Patient-centred self-administered acupressure intervention

Pre-selected Acupoints (Acupoints on which ALL participants must perform acupressure)				
Acupoint	**Location**	**Functions**	**Stimulating motion**	**Frequency**
Neiguan (PC6, 內關穴)	On the anterior aspect of the forearm, between the tendons of the palmaris longus and the flexor carpi radialis, 2 cun proximal to the palmar wrist crease	Wide disease spectrum including pain, cardiovascular disorders and digestive diseases. Has a strong effect on regulating the function of the autonomic nervous system and thus commonly used for pain, weakness, fatigue and depression.	Using thumb pad rub the area bilaterally of the acupoint on the wrist clockwise or anticlockwise	60/min for each side
Zusanli (ST36, 足三里)	On the anterior lateral side of the leg at 3 cun below the knee joint, one middle finger breadth from the anterior crest of the tibia	Broad therapeutic effects, from gastro, intestinal and endocrinal diseases to neuropsychiatric disorders. Widely used for fatigue management and pain alleviation for different patient groups for years. Stimulation at Zusanli evokes the robust response in limbic-paralimbic-neocortical network involved in autonomic, pain, mood and cognitive function.	Using thumb pad firmly massage the area bilaterally on the anterior lateral side of the leg, 3 cun below the knee joint	60/1.5 mins for each side
Sanyinjiao (SP6, 三陰交)	On the tibial aspect of the leg, posterior to the medial border of the tibia, 3 cun superior to the prominence of the medial malleolus	60/min	Using thumb pad firmly massage the area bilaterally on the medial border of the tibia	60/min for each side
Baihui (DU20, 百會)	On the vertex of the head at the sigittal midline of the scalp at the midpoint of the line connecting the apexes of both ears	Treatment of various mental disorders, in particular insomnia, depression, anxiety, headache and decreased memory.	Using four finger pads gently tap the area of this acupoint on the scalp	

Additional Acupoints (Acupoints from which trainers can recommend the TWO most effective to accommodate patients' individual needs)				
Acupoint	**Location**	**Functions**	**Stimulating motion**	**Frequency**
Shenmen (HT7, 神門)	On the anteromedial aspect of the wrist, radial to the flexor carpi ulnaris tendon, on the palmar wrist crease	Chiefly for calming the mind and tranquilising the spirit. Used for a variety of psychogenic conditions including sleep disturbance/ insomnia, anxiety and depression. Also functions to regulate cardiac functions.	Using thumb pad rub the area bilaterally of the acupoint on the wrist clockwise or anticlockwise	60/min for each side
Hegu (LI4, 合谷)	On the dorsum of the hand, between the first and second metacarpal bones, in the middle of the second metacarpal bone on the radial side	Expels wind and releases the exterior, tonifies *qi* and strengthens immunity; used to manage every type of pain and psychogenic tension.	Using thumb pad firmly massage the surrounding area of this acupoint on the dorsum of the hand unilaterally	30/min for each side
Taichong (LV3, 太衝)	On the dorsum of the foot, between the first and second metatarsal bone, in the depression distal to the junction of the bases of the two bones, over the dorsalis pedis artery	Can be used for various kinds of pain, especially for headache and visceral pain. Great points for psychological disorders, depression and anxiety in particular.	Using one thumb press on the points bilaterally while the other four fingers should hold the centre of the foot palm	30/min for each side
Taixi (KI3, 太溪)	On the posteromedial aspect of the ankle in the depression between the prominence of the medial malleolus and the calcaneal tendon	Widely used for regulating the endocrine system. Suitable for relieving fatigue and toothache. In TCM, functions to replenish kidney yin.	Using one thumb press on the points bilaterally while the other four fingers should hold the anterior of exterior ankle	15/min for each side
Fengchi (GB20, 風池)	On the nape, in a depression between the upper portion of the sternocleidomastoid muscle and the trapezius	A commonly used point for acupressure to treat headache, neck and shoulder pain and stiffness. Also, beneficial in relieving convulsion, agitation, insomnia and stress-related symptoms.	Using two thumbs press on the points bilaterally while the other four fingers should hold the back of the head naturally	60/min
Guanyuan (RN4, 關元)	On the lower abdomen on the anterior midline at 3 cun below the centre of the umbilicus, respectively	Often applied together in acupressure to tonify *qi* because essential *qi* (元氣) is housed and circulated in these two points. Beneficial for constipation, retention of	Using finger pads in a clockwise circle gently massage the lower abdomen area, 3 cun below the umbilicus	200/2 mins

Qihai (RN6, 氣海)	On the lower abdomen on the anterior midline at 1.5 cun below the centre of the umbilicus, respectively	urination, frequent nocturia, indigestion and fatigue. Modulate the limbic-medial prefrontal network related to cognitive function.		
Shenshu (BL23, 腎俞)	On the low back at 1.5 cun lateral to the posterior midline at the level of the second lumbar vertebral spine	Well known for all kidney-related issues which affect the brain, bone, hair, teeth and/or hearing. Useful for deficiency conditions: exhaustion, weakness, chronic fatigue, good point for the elderly as kidney *jing* is naturally depleted.	Using the fists gently tap the lumbar area of this acupoint at the low back bilaterally	60/1.5 mins

Note. 1 cun equals the width of the patient's thumb.

Appendix 2. Training content

Time allocation **(120 min/session)**	**First Training Session**	**Second Training Session**
10 min	Ice-breaking and introduction of the training	Warm up and review of the individualised protocol with the patient
15 min	An overview of the acupoints	Demonstration of the protocol by trainers
30 min	Demonstration by trainers with the use of training materials, with emphasis on the acupoints' location, functions, appropriate level of pressure to apply on the acupoints and the proper stimulating motion	Return demonstration by the patient under supervision; Trainers providing feedback and clarifying the patient's concerns if any; Refining the acupressure protocol if necessary
15 min	Practice of the pre-selected acupoints by the patient	
15 min	Selection of two additional acupoints based on patient preference under guidance of trainers	Practice by the patient until he or she is deemed proficient
25 min	Return demonstration of the entire individualised protocol (four pre-selected and two self-selected acupoints) by the patient	Assessing the patient's skills with the use of a competency checklist
10 min	Wrapping up the session and encouraging the patient to try out the protocol in his or her spare time	Teaching the patient to fill in the acupressure diary and concluding the training

Appendix 3. Competency checklist

Patient-centred self-administered acupressure: Participant competency assessment

Name of participant: _____

Assessment date: _____

Please put a ✓ if the participant demonstrates competency in the corresponding category.

Acupoint	Correctly located	Stimulating motion	Appropriate pressure (achieved *deqi*)	Frequency
Neiguan (PC6, 內關穴)				
Zusanli (ST36, 足三里)				
Sanyinjiao (SP6, 三陰交)				
Baihui (DU20, 百會)				
Shenmen (HT7, 神門)				
Hegu (LI4, 合谷)				
Taichong (LV3, 太衝)				
Taixi (KI3, 太溪)				
Fengchi (GB20, 風池)				
Guanyuan (RN4, 關元)				
Qihai (RN6, 氣海)				

Total marks: _____out of 44

Name of assessor: _____

Signature: _____

Appendix 4. Definitions of feasibility- and acceptability-related outcomes

Parameters	Assessment method	Goal (if any)
Eligibility rate	The number of participants who met the inclusion criteria divided by the number of people screened for eligibility.	NA
Recruitment rate	The number of participants who consented to participate in the study divided by the number of participants who met the inclusion criteria.	NA
Adherence rate	The number of participants who have attended both training sessions and at least two out of three follow-up sessions, as well as performing self-administered acupressure at least once daily throughout the intervention period, divided by the number of intervention group participants who completed the study (goal > 80%)	≥ 80%
Retention rate	The number of participants who completed the study divided by the number of randomised participants (goal > 70%). Reasons for drop-out were recorded.	≥ 80%
Participant satisfaction	An investigator-designed questionnaire regarding participants' experience of and satisfaction with the study	NA
Adverse events	Records in training logbook	None

Appendix 5. Participant satisfaction results

Quantitative survey items	Intervention group (n = 11) Agree or strongly agree, n (%)	Health education group (n = 7)[a] Agree or strongly agree, n (%)
1. I enjoyed the intervention sessions.	11 (100%)	7 (100%)
2. I will recommend the intervention to other patients.	8 (72.7%)	6 (85.7%)
3. The intervention improved my health.	6 (54.5%)	5 (71.4%)
4. Did you feel uncomfortable due to the intervention? (Indicating 'no')	11 (100%)	7 (100%)
I was satisfied with:		
5. The coach	11 (100%)	7 (100%)
6. The research staff	11 (100%)	7 (100%)
7. Class content	10 (90.9%)	7 (100%)
8. Class schedule	10 (90.9%)	7 (100%)
9. Class venue	11 (100%)	7 (100%)
10. Class frequency	11 (100%)	6 (85.7%)
11. Data collection	11 (100%)	5 (71.4%)
12. The class logistics as a whole	11 (100%)	6 (85.7%)
Qualitative feedback categories	Intervention group (n = 11)	Health education group (n = 7)[a]
Acupoint(s) that you think work the best:	Baihui (n = 3), Hegu (n = 2); Qihai, Zusanli	Fengchi, Neiguan, Zusanli, Sanyinj, Baihui, Hegu, Taixi, Guanyuan, Qihai, Shenshu
Positive feedback:	Sleep much better, less fatigue, digestion better, feel more relaxed	Sleep better, headache relieved, digestion improved
Suggestions for improvement:	Want more acupoints (n = 4), want to learn acupoints that relieve knee pain, want dietary advice as well, prefer group class, prefer acupoints that are on upper limbs as they are easier to massage	Want more sessions (n = 2), want more acupoints, prefer acupoints that are on upper limbs as they are easier to massage, prefer group class

[a]The health education group participants were invited to complete the questionnaire after they received the same acupressure intervention during the post-study period.