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Electroacupuncture trigeminal nerve stimulation plus body acupuncture for chemotherapy-induced cognitive impairment in breast cancer patients: An assessor-participant blinded, randomized controlled trial

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ABSTRACT

Chemotherapy causes various side effects, including cognitive impairment, known as 'chemobrain'. In this study, we determined whether a novel acupuncture mode called electroacupuncture trigeminal nerve stimulation plus body acupuncture (EA/TNS + BA) could produce better outcomes than minimum acupuncture stimulation (MAS) as controls in treating chemobrain and other symptoms in breast cancer patients. In this assessor- and participant-blinded, randomized controlled trial, 93 breast cancer patients under or post chemotherapy were randomly assigned to EA/TNS + BA (n = 46) and MAS (n = 47) for 2 sessions per week over 8 weeks. The Montreal Cognitive Assessment (MoCA) served as the primary outcome. Digit span test was the secondary outcomes for attentional function and working memory. The quality of life and multiple functional assessments were also evaluated. EA/TNS + BA treated group had much better performance than MAS-treated group on reverse digit span test at Week 2 and Week 8, with medium effect sizes of 0.53 and 0.48, respectively, although no significant differences were observed in MoCA score and prevalence of chemobrain between the two groups. EA/TNS + BA also markedly reduced incidences of diarrhoea, poor appetite, headache, anxiety, and irritation, and improved social/family and emotional wellbeing compared to MAS. These results suggest that EA/TNS + BA may have particular benefits in reducing chemotherapy-induced working memory impairment and the incidence of certain digestive, neurological, and distress-related symptoms. It could serve as an effective intervention for breast cancer patients under and post chemotherapy (trial registration: https://www.clinicaltrials.gov: NCT02457039).

Abbreviations: 5-HT, serotonin; ADHD, attention-deficit/hyperactivity disorder; ANOVA, analysis of variance; EA/TNS+BA, electroacupuncture trigeminal nerve stimulation plus body acupuncture; FAACT, Functional Assessment of Anorexia/Cachexia Therapy; FACT-B, Functional Assessment of Cancer Therapy-Breast Cancer; FACT-BRM, Functional Assessment of Cancer Therapy-Biologic Response Modifier; FACT-Taxane, Functional Assessment of Cancer Therapy-Taxane; FCIT, Functional Assessment of Chronic Illness Therapy; IRB, Institutional Review Board; MAS, minimum acupuncture stimulation; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; NA, noradrenaline; OC, observed cases; OCD, obsessive–compulsive disorder

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1. Introduction

Although the development of various chemotherapeutic drugs has greatly improved clinical outcomes and survival rate of cancer patients, it also causes broad adverse side effects, including chemotherapy-induced cognitive impairment, known as chemobrain. Chemobrain has drawn increasing attention due to the rise in the number of cancer survivors over the past two decades (Nelson et al., 2007). Numerous studies have shown that chemotherapy can cause acute and long-term post-treatment cognitive impairment, often manifesting as decreased memory, forgetfulness, difficulty in learning, attention, concentration and coordination of multitasking and organization (Asher, 2011). Over 75% cancer patients reported to experience acute cognitive symptoms during chemotherapy and 17%–34% of them have long-term post-treatment cognitive deficits which can persist up to 10 years (Hede, 2008). Breast cancer survivors displayed higher prevalence of post-treatment cognitive impairment (Matsuda et al., 2005). The severity of reported chemobrain symptoms is variable, from subtle to more severe (Asher, 2011). Chemobrain has become an apparent quality-of-life issue for survivors (Asher, 2011). There are no effective interventions available to prevent and treat chemobrain, although some pharmacological and cognitive approaches have been tested (Avisar et al., 2012).

As an ancient therapeutic technique, acupuncture therapy has been increasingly introduced into the management of cancer treatment-related symptoms. A large body of evidence has confirmed that acupuncture is effective in reducing side effects of chemotherapy, including pain, nausea, hot flashes, fatigue, xerostomia, anxiety, depression, and sleep disturbance (Garcia et al., 2013). Acupuncture is also beneficial in improving cognitive dysfunction occurred in patients with mild cognitive impairment (MCI) and dementia (Chou et al., 2009; Guo et al., 2002; Yu et al., 2006; Zhao et al., 2009; Zhou and Jin, 2008) and in various animal models (Manni et al., 2009; Yu et al., 2005a,b). Recently, transcutaneous trigeminal nerve stimulation has been confirmed to be effective in treating depression, epilepsy, and attention-deficit/hyperactivity disorder (ADHD) (Cook et al., 2016; DeGiorgio et al., 2013; McGough et al., 2019; Schrader et al., 2011). We then have developed a novel acupuncture mode called electroacupuncture trigeminal nerve stimulation (EA/TNS) in which electrical stimulation is conducted on forehead acupoints that are innervated by V1 trigeminal branches (Zhang et al., 2012b). We have demonstrated the effectiveness and benefits of EA/TNS in the treatment of post-stroke cognitive impairment, depression, insomnia, and obsessive–compulsive disorder (OCD) (Chung et al., 2012; Man et al., 2014; Zhang et al., 2009, 2012a, 2020). There are therefore reasons to hypothesize that a combination of EA/TNS and body acupuncture (EA/TNS + BA) could yield significant benefits in the prevention and treatment of chemobrain and other side effects associated with cancer and chemotherapy.

To test this hypothesis, this study sought to determine whether EA/TNS + BA could produce better clinical outcomes in improving chemobrain and other related symptoms in breast cancer patients under and post chemotherapy in comparison with minimum acupuncture stimulation (MAS) as controls using assessor- and participant-blind, randomized controlled design.

2. Methods

2.1. Settings and subjects

This assessor- and participant-blind, randomized controlled trial was conducted between October 2015 and December 2018 in clinics of the School of Chinese Medicine of the University of Hong Kong. Potentially eligible patients were recruited through clinical oncologists' referral from local hospitals and advertisement. The study protocol was approved by Institutional Review Board (IRB) of the University of Hong Kong and registered in https://clinicaltrials.gov/ct2/show/NCT02457039 (NCT02457039) on May 29, 2015 before the first participant was recruited. All participants gave voluntary, written, informed consent before entering the trial.

2.2. Inclusion and exclusion criteria

Patients were eligible for the study if they met all the following criteria: (1) Chinese females aged 18 to 65 years; (2) had a diagnosis of stage I-IIIa breast cancer; and (3) were under chemotherapy or the time did not exceed 2 weeks after the completion of chemotherapy.

Subjects were excluded from the study if they had: (1) epilepsy or other unstable medical conditions; (2) investigational drug treatment within the past 6 months; (3) alcoholism or drug abuse within the past 1 year; (4) severe needle phobia; (5) heart pacemaker or other electronic devices implanted in the body; or (6) bleeding tendency.

2.3. Randomization and blinding

Following conformance of patients' eligibility, they were randomly assigned to either EA/TNS + BA or MAS in a ratio of 1:1 based on random codes which were simple, complete, non-sequential numbers and produced in advance using a computer-generated random block. The group allocation was done by an acupuncturist (C.Y.Y.) in a partially double-blind manner, i.e., the random codes were only known by the acupuncturists (L.L.Y. and C.Y. Y.). The clinical assessor (S.C.M.) was arranged to conduct assessment in different days from acupuncture treatment so as to avoid cross communication among the assessor, acupuncturists, and participants. The assessor was also instructed not to acquire participant's treatment information and their needling feelings.

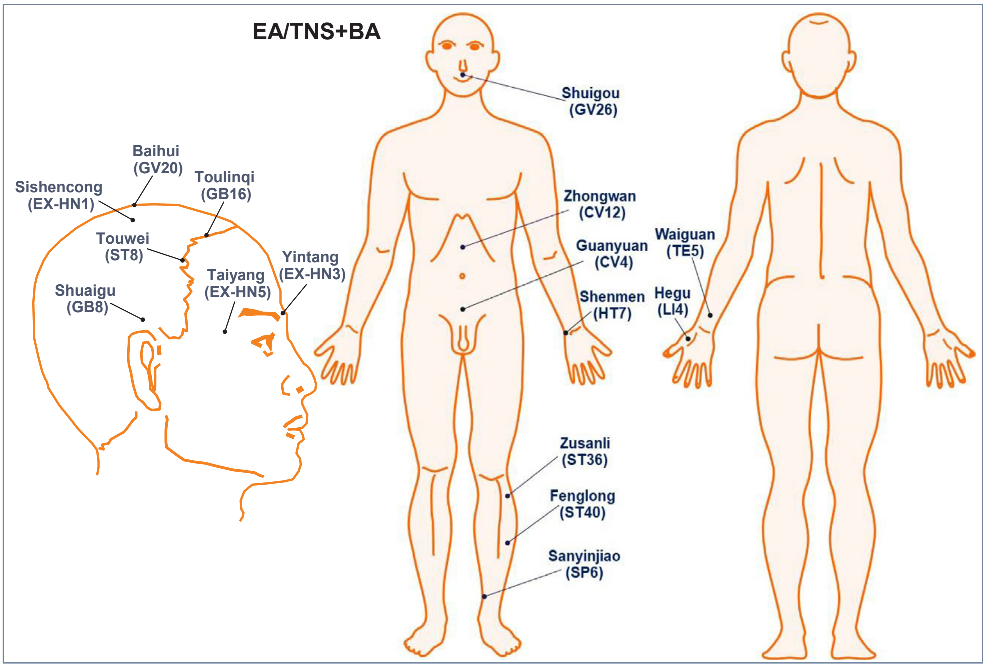
It has been suggested that different information disclosure may affect blinding and trial outcomes (Cheon et al., 2018). In participant information leaflets and informed consent, we therefore made the statement that participants would randomly receive one of the two different acupuncture regimens, but did not provide information about differences in number of acupoints and stimulation modes of the two regimens so as to diminish potential differences caused in participants' expectation to acupuncture treatment. In addition, to further validate the blinding design, acupuncturists were instructed not to communicate with participants during the treatment; participants were instructed to lie supine with the eyes closed so that they could not visualize acupuncture procedure.

2.4. Treatment

2.4.1. Acupuncture intervention

Acupuncture intervention was conducted for 2 sessions per week over 8 consecutive weeks. The determination of 8 weeks of the treatment duration was based on the fact that the robust effects of acupuncture in cancer patients were generally observed within 8 weeks of treatment (Zhang et al., 2010). A brief introduction of acupuncture procedure was given by acupuncturists during first visit. All sessions of acupuncture treatment for a participant were performed by the same acupuncturist in order to eliminate deviations from different acupuncturists. Acupoints used for EA/TNS + BA and MAS are illustrated in Fig. 1.

For EA/TNS + BA, the following 15 body acupoints with only manual stimulation were used: Shenmen (HT7), Hegu (LI4), Waiguan (TE5), Zusanli (ST36), Fenglong (ST40) and Sanyinjiao (SP6) in two sides, and Zhongwan (CV12), Guanyuan (CV4), and Shuigou (GV26) in midline. Meanwhile, electrical stimulation was conducted on six pairs of the forehead acupoints with positive (+) and negative (−) electrode cord connection as follows: Baihui (GV20, +) and Yintang (EX-HN3, −), left Sishencong (EX-HN1, −) and Toulinqi (GB15, +), right Sishencong (EX-HN1, −) and Toulinqi (GB15, +), bilateral Shuaigu (GB8, L+, R−), bilateral Taiyang (EX-HN5, L+, R−), and bilateral Touwei (ST8, L+, R−). The determination of these acupoints are based on modern neurobiological rationales and traditional Chinese medicine



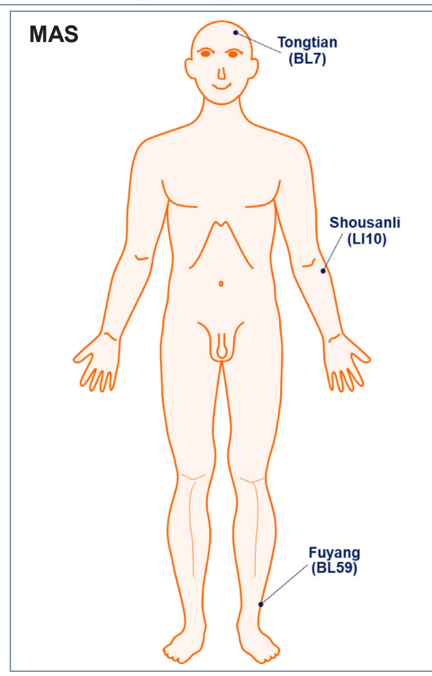


Fig. 1. Acupoints used in electroacupuncture trigeminal nerve stimulation plus body acupuncture (EA/TNS + BA) and minimum acupuncture stimulation (MAS) as controls.

(TCM) theory as previously reported (Zhang et al., 2012a, 2012b, 2020).

Disposable acupuncture needles (0.30 mm in diameter and 25–40 mm in length) were inserted at a depth of 10–30 mm perpendicularly or obliquely into acupoints. Manual manipulation was carried out for all acupoints to evoke needling sensation. Electrical stimulation was additionally delivered on the 6 pairs of the frontal acupoints. The output peak current and voltage of the machine (model: ITO ES-360) were 6 V and 48 mA, respectively, with constant wave at frequency of 2 Hz and phase duration of 100 µs for 30 min. The stimulation intensity was adjusted to a level at which patients felt most comfortable. The use of the low frequency rather high frequency was because it could modulate biochemical adaptation of the brain in more favourable manner in improving cognitive functions (Han, 2003). Electrical stimulation lasted 30 min. The needles on body acupoints were also retained for 30 min.

For MAS, the following 6 acupoints were used: bilateral Tongtian (BL7, L+, R−), bilateral Shousanli (LI10), and bilateral Fuyang (BL59). Electrical stimulation was only performed on bilateral Tongtian (BL17) and the parameters are the same as above, but the intensity were adjusted to a level at which patients just started feeling stimulation. The choice of this control regimen was based on the following two reasons: (1) The acupoints used are unrelated or less related to the treated syndromes according to traditional Chinese medicine (TCM) theory; and (2) the number of acupoints used and the intensity of electrical stimulation are kept to a minimum level at which patients were aware of receiving active acupuncture treatment.

Acupuncture procedure was conducted by Chinese medicine

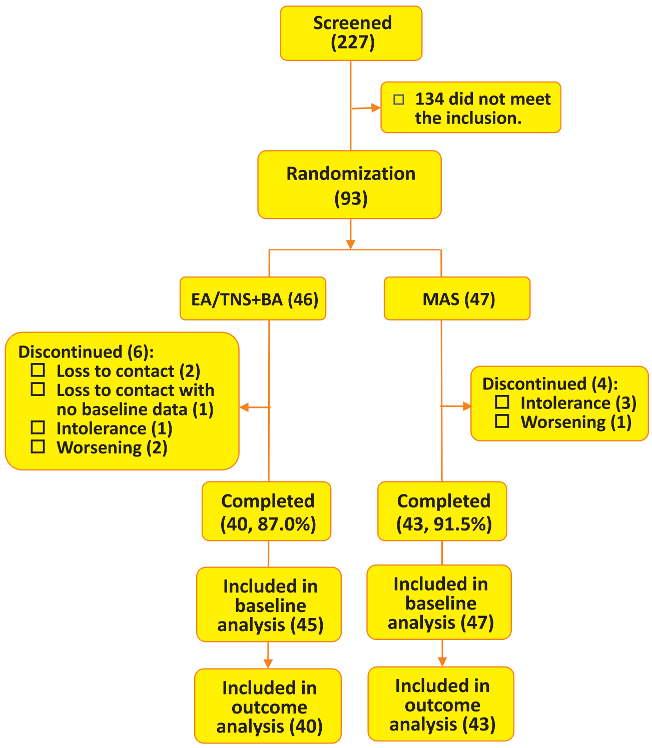


Fig. 2. Flowchart of screening and patient recruitment. EA/TNS + BA, electroacupuncture trigeminal nerve stimulation plus body acupuncture; MAS minimum acupuncture stimulation.

Table 1
Baseline characteristics.

Variables	EA/TNS + BA (n = 45)	MAS (n = 47)	*P* value[a,b]
Age (y) [a]	47.9 ± 9.7	47.9 ± 10.6	0.174
Marital status, n (% [b]			
Single/divorce/widow	13 (28.9)	19 (40.4)	0.346
Married	32 (71.1)	28 (59.6)	
Education, n (%)[b]			
Primary	3 (6.7)	4 (8.5)	0.939
Secondary	23 (51.1)	23 (48.9)	
College and above	19 (42.2)	20 (42.6)	
Household income, n (%)[b,c]			
Low	7 (15.6)	5 (10.6)	0.232
Middle	34 (75.6)	32 (68.1)	
High	4 (8.8)	10 (21.3)	
Duration of illness (months)[a]	10.8 ± 23.8	6.4 ± 24.6	0.308
Breast cancer stage, n (%) [b]			
I	6 (13.3)	10 (21.3)	0.574
II	25 (55.6)	25 (53.2)	
IIIa	14 (31.1)	12 (25.5)	
Under or post chemotherapy at entry, n (%)[b]			
Under	33 (73.3)	37 (78.7)	0.718
Post	12 (26.7)	10 (21.3)	
Regular drinker, n (%)[b,d]	17 (37.8)	16 (34.0)	0.876
Regular smoker, n (%)[b,e]	1 (2.2)	2 (4.3)	0.969
Previous acupuncture experience, n (%)[b]	25 (55.6)	37 (78.7)	0.131

[a]Continuous data are expressed as mean ± SD and examined using Student *t*-test.
[b]Categorical data were examined using Chi-square (χ^2) or Fisher Exact test.
[c]Compared to average household incomes of local communities.
[d]Regular drinkers were those who had had at least 4 alcoholic drinks weekly for one year.
[e]Regular smokers were those who had smoked every day for at least one year.
EA/TNS + BA, electroacupuncture trigeminal nerve stimulation plus body acupuncture; MAS, minimum acupuncture stimulation.

Table 2
Neo-adjuvant chemotherapy regimen profile.

Variables [b]	EA/TNS + BA (n = 45)	MAS (n = 47)	*P* value [a]
FEC-T	9 (20.0)	11 (23.4)	0.652
TAC	7 (15.6)	7 (14.9)	
TC	12 (26.7)	9 (19.0)	
AC	2 (4.4)	0	
TPH	11 (24.4)	15 (31.9)	
Others	4 (8.9)	5 (10.6)	

[a]Chi-square (χ^2) test was used to test.
[b]EA/TNS + BA, electroacupuncture trigeminal nerve stimulation plus body acupuncture; MAS, minimum acupuncture stimulation.
FEC-T, 5-Fluorouracil + Epirubicin + Cytoxan (cyclophosphamide) + Taxotere (docetaxel).
TAC, Taxotere (docetaxel) + Adriamycin (doxorubicin) + Cytoxan (cyclophosphamide).
TC, Taxotere (docetaxel) + Cytoxan (cyclophosphamide).
AC, Adriamycin (doxorubicin) + Cytoxan (cyclophosphamide).
TPH, Taxotere (docetaxel) + Paraplatin (carboplatin) + Herceptin (trastuzumab).

practitioner (L.L.Y. and C.Y. Y.) who had had over 5 years of experience in acupuncture practice.

2.4.2. Chemotherapy and other therapies

For participants who were under chemotherapy, they continued their chemotherapeutic regimens as usual. The most commonly used regimens were Cytoxan (cyclophosphamide)-containing regimens. Other therapies, such as surgery, hormone therapy, and radiotherapy were also allowed as usual.

2.5. Assessment

2.5.1. Treatment outcomes

The primary outcome was measured using the Montreal Cognitive Assessment (MoCA) which has been extensively used in the study of cognitive disorders (Nasreddine et al., 2005). Since MoCA subscales are not sensitive to subtle changes in attentional function and working memory (Koski, 2013), the forward and reverse digit span test served the secondary outcomes to detect attentional function and working memory (Meagher et al., 2015). In addition, EORTC QLQ-C30 and BR23 (V3) was used to examine the quality of life of breast cancer patients (Cante et al., 2013). Functional changes and side effects associated with therapies were measured using the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B), Functional Assessment of Chronic Illness Therapy (FACIT), Functional Assessment of Anorexia/Cachexia Therapy (FAACT), Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane), and Functional Assessment of Cancer Therapy-Biologic Response Modifier (FACT-BRM). these instruments have been widely used in breast cancer patients (Montazeri, 2008; Cella et al., 2003). Most items of these functional assessments are 5-point Likert scale questions. Functional items which were rated as "3″ (quite a bit) or higher and incidences were significantly different between the two groups in any assessment point were extracted for statistical analysis (see below).

Assessments were conducted at baseline and once biweekly thereafter. A pre-trial training workshop was carried out to ensure consistency of assessments. In most cases, all assessments of a subject from baseline to endpoint were conducted by the same assessor (S.C.M.).

2.5.2. Credibility of the blinding

We also assessed the credibility of the blinding design on EA/TNS + BA and MAS procedure after the completion of the last assessment as reported previously (Fink et al., 2001; Zhang et al., 2012a). A participant was asked for the following question: "As we informed you that you had an equal chance of receiving EA/TNS + BA or MAS, which

Table 3
Treatment outcome analysis of cognitive performance in breast cancer patients.

Variables[a]	EA/TNS + BA (n = 40)	P value[b]	MAS (n = 43)	P value[b]	Between-group Difference	Between-group Effect Size	P value[c]
MoCA[d]							
Baseline	0.3 (−0.3 to 0.8)	0.031	0.4 (−0.2 to 0.9)	0.193	−0.1 (−0.9 to 0.7)	−0.16	0.826
Week 2	2.5 (2.0 to 3.1)	< 0.001	2.1 (1.6 to 2.7)	< 0.001	0.4 (−0.4 to 1.1)	0.17	0.340
Week 4	2.6 (2.0 to 3.1)	< 0.001	2.3 (1.8 to 2.9)	< 0.001	0.3 (−0.5 to 1.0)	0.12	0.503
Week 6	3.1 (2.5 to 3.6)	< 0.001	3.1 (2.6 to 3.6)	< 0.001	0 (−0.8 to 0.8)	−0.02	0.999
Week 8	3.2 (2.7 to 3.8)	< 0.001	3.0 (2.5 to 3.6)	< 0.001	0.2 (−0.6 to 1.0)	0.12	0.634
Forward digit span test							
Baseline	0.6 (0.3 to 1.0)	< 0.001	0.4 (0.1 to 0.7)	< 0.001	0.2 (−0.7 to 0.3)	0.28	0.395
Week 2	0.9 (0.6 to 1.2)	< 0.001	0.8 (0.5 to 1.2)	< 0.001	0.1 (−0.4 to 0.5)	0.08	0.837
Week 4	1.2 (0.8 to 1.5)	< 0.001	0.9 (0.6 to 1.2)	< 0.001	0.3 (−0.2 to 0.7)	0.27	0.284
Week 6	1.0 (0.6 to 1.3)	< 0.001	1.1 (0.8 to 1.4)	< 0.001	−0.2 (−0.6 to 0.3)	−0.11	0.512
Week 8	1.3 (0.9 to 1.6)	< 0.001	1.2 (0.9 to 1.6)	< 0.001	0 (−0.4 to 0.5)	0.07	0.909
Reverse digit span test							
Baseline	0.6 (0 to 1.3)	0.058	0.6 (−0.1 to 1.2)	0.084	0.1 (−0.8 to 1.0)	0.05	0.867
Week 2	1.8 (1.2 to 2.5)	< 0.001	0.9 (0.3 to 1.5)	0.006	0.9 (0 to 1.8)	0.53	0.045
Week 4	2.0 (1.4 to 2.7)	< 0.001	1.3 (0.6 to 1.9)	< 0.001	0.7 (−0.2 to 1.6)	0.33	0.113
Week 6	2.1 (1.4 to 2.7)	< 0.001	1.4 (0.8 to 2.0)	< 0.001	0.7 (−0.2 to 1.6)	0.29	0.149
Week 8	2.6 (1.9 to 3.2)	< 0.001	1.3 (0.6 to 1.9)	0.001	1.3 (0.4 to 2.2)	0.48	0.004

[a] Values are adjusted means and 95%CI.
[b] Compared to baseline value within group.
[c] Compared between the two groups at the same time point.
[d] EA/TNS + BA, electroacupuncture trigeminal nerve stimulation plus body acupuncture; MAS, minimum acupuncture stimulation; MoCA, Montreal Cognitive Assessment.

do you think you had received?" The participant would answer: EA/TNS + BA, MAS, or "unknown".

2.6. Data analysis

Previous studies have revealed that acupuncture could produce a 20%-30% improvement on mild cognitive impairment (Chou et al., 2009; Guo et al., 2002; Yu et al., 2006; Zhao et al., 2009; Zhou and Jin, 2008). A sample size of 46 each group of this study would be sufficient to detect a 30% difference in the prevalence of chemobrain between the two groups at an 80% power and a statistical level of 0.05.

The primary outcome, MoCA, and the secondary outcomes, forward and reverse digit span test data were analysed based on observed cases (OC), defined as a subset of subjects who had completed 8-week treatment and all assessments as per protocol. The data were transformed as changes from the lowest score, all of which were observed in baseline or Week 2 assessments, A linear mixed-effect model for repeated-measures analysis was used, in which treatment, time point, and the interaction between treatment and time point were set as fixed effects; individual patient was set as the random effects; and age was adjusted as a covariate in the model. Typically, we used first-order autoregressive model as the covariance structure for all repeated-measures data.

Between-group effect size was calculated by dividing the between-group difference in post-treatment means with the pooled standard deviation. The effect sizes of 0.20, 0.50, 0.80, and 1.30 represent "small", "medium", "large", and "very large" effect, respectively (Borenstein, 1997).

The prevalence of chemobrain, which is defined as a MoCA score of < 26, was calculated and examined using Chi-square (χ^2). Chi-square (χ^2) or Fisher Exact test was also used to examine categorical baseline variables and incidence of functional assessments items. Student *t*-test was applied to examine between-group differences in continuous baseline variables.

James' blinding index (JBI) was calculated to assess the successfulness of blinding (James et al., 1996). This index ranges from 0 to 1, 0 being total lack of blinding, 1 being complete blinding and 0.5 being completely random blinding. If the upper bound of the confidence interval of JBI is low 0.5, the study is regarded as lacking blinding. Otherwise, one may conclude that there is insufficient evidence for unblinding (James et al., 1996).

All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC) and Stata (version 13.1; StataCorp, College Station, Texas) with 2-sided $p < 0.05$ considered significant.

3. Results

3.1. Baseline characteristics of participants

Of 227 patients screened, 93 participants were randomly assigned to EA/TNS + BA (n = 46) and MAS (n = 47) group; 83 (89.2%) completed all treatments and assessments as per protocol and were included in treatment outcome analysis (Fig. 2). One participant who had been randomized to EA/TNS + BA group, but was lost to contact without baseline data was excluded in data analysis. All baseline variables were not different between the two groups (Table 1).

3.2. Chemotherapeutic profiles

There were 76.1% (70/92) participants who were under chemotherapy treatment at entry (Table 1). The majority (62.0%, 57/92) of participants were treated with cyclophosphamide (Cytoxan)-contained regimens. No significant difference in chemotherapeutic profiles was observed between the two groups (Table 2).

3.3. Efficacy

3.3.1. Cognitive variables

Changes in score on MoCA, forward and reverse digit span test over time are illustrated in Table 3 and Fig. 3. A linear mixed-effects model revealed no significant interaction between group and time on the three variables ($F = 0.550$, $P = 0.702$ on MoCA; $F = 0.680$, $P = 0.604$ on forward digit span test; $F = 1.350$, $P = 0.251$ on reverse digit span test). Significant time main effects were observed on all the three variables ($F \geq 4.98$, $P \leq 0.0007$). Significant group main effects were present on reverse digit span test ($F = 7.030$, $P = 0.009$), but not MoCA ($F = 0.280$, $P = 0.596$) and forward digit span test ($F = 0.290$, $P = 0.592$). Between-group comparisons further showed that EA/TNS + BA group had markedly higher correct score on reverse digit span test than MAS group at Week 2 ($P = 0.045$) and Week 8

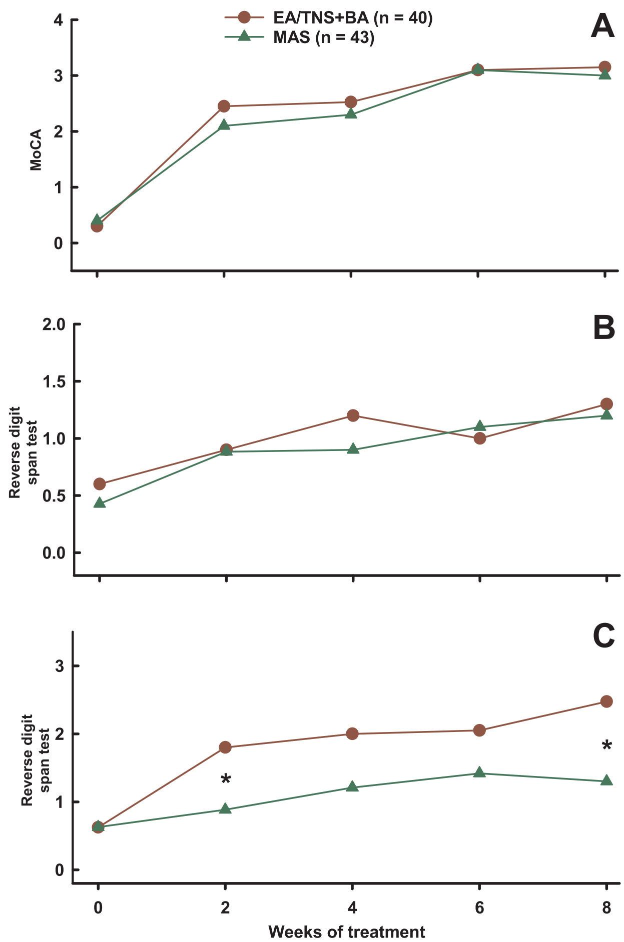


Fig. 3. The effects of electroacupuncture trigeminal nerve stimulation plus body acupuncture (EA/TNS + BA) and minimum acupuncture stimulation (MAS) on changes in the Montreal Cognitive Assessment (MoCA) (A), forward digit span test (B), and reverse digit span test (C) from the lowest scores all of which were observed in baseline and Week 2. * indicates a significant difference between the two groups at an assessment point tested with a linear mixed-effect model.

Table 4
The prevalence of chemobrain over 8 weeks of the treatment.[a]

	EA/TNS + BA (N = 40), n (%) [b]	MAS (N = 43), n (%) [b]	*P* value [c]
Baseline	22 (55.0)	22 (51.2)	0.897
Week 2	6 (15.0)	11 (25.6)	0.357
Week 4	6 (15.0)	11 (25.6)	0.357
Week 6	1 (2.5)	4 (9.3)	0.361
Week 8	2 (5.0)	3 (7.0)	0.912

[a]Chemobrain is defined as a MoCA score of < 26.
[b]EA/TNS + BA, electroacupuncture trigeminal nerve stimulation plus body acupuncture; MAS, minimum acupuncture stimulation.
[c]Data were examined using Chi-square (χ^2) test.

($P = 0.004$) (Fig. 3C), with effect sizes of 0.53 and 0.48, respectively.

3.3.2. Prevalence of chemobrain

At baseline, 54.3% (50/92) of participants met the criteria of chemobrain. The prevalence of chemobrain was not significantly different between the two groups at all the measurement points (Table 4).

3.4. Incidences of adverse events and functional items

The incidences of adverse events and functional items that were significantly different between the two groups are summarized in Table 5. The EA/TNS + BA group had significantly fewer incidents of diarrhea ($P = 0.037$), tenseness ($P = 0.030$), worrisome ($P = 0.018$), and irritation ($P = 0.040$) reported at Week 4, and headache ($P = 0.042$) and tinnitus ($P = 0.026$) reported at Week 8 than MAS group.

The EA/TNS + BA group had a significantly higher proportion of participants who complained difficulty eating rich or "heavy" foods at baseline than MAS group ($P = 0.030$), but there were no significant differences at Week 4 and Week 8.

There were many more participants who were satisfied with how they were dealing with their illness and whose family members had accepted their illness in the EA/TNS + BA group than the MAS group at Week 4.

3.5. Credibility of the blinding design

Among 83 participants who had completed all assessments as per protocol, 7.2% (6/83) did not answer the credibility assessment question without any reason. Among the remaining 77 participants who responded to the blinding assessment, 74% (57/77) were unsure of their treatment allocation; 27.8% (10/36) in EA/TNS + BA and 4.9% (2/41) in MAS believed that they received EA/TNS + BA treatment. The JBI was 0.79 (95%CI: 0.72 to 0.87), indicating a high successfulness of blinding.

4. Discussions

The principal finding of this study is that the EA/TNS + BA group had much better performance in reverse digit span test at certain measurement points compared to the MAS-treated group, with medium effect size of 0.48–0.53, although the two groups were not different in MoCA, forward digit span test, and prevalence of chemobrain. Digit span test is specifically designed to examine working memory, whereas MoCA represents overall cognitive performance (Koski, 2013; Meagher et al., 2015). A large number of studies have suggested that chemotherapy is more apparent in impairing working memory (Asher, 2011; Cheng et al., 2017). It is well evidenced that acupuncture has particular effects in improving working memory performance (Bosch et al., 2015; Bussell, 2013). This could, at least partially, explain the differential effects of EA/TNS + BA on digit span test and MoCA observed in this study. Most recently, our two trials also have revealed the effectiveness of EA/TNS + BA and acupuncture intervention in patients with post-stroke cognitive impairment (Yang et al., 2019; Zhang et al., 2020). It appears that EA/TNS + BA may be particularly beneficial in improving chemotherapy-induced impairment of working memory.

Additionally, we showed a 54.3% overall prevalence of chemobrain at baseline, and most was mild cognitive impairment with an average overall MoCA score of 25.8. This is consistent with previous studies in breast cancer population (Matsuda et al., 2005).

The present study further revealed that the EA/TNS + BA group was also more effective than MAS in reducing the incidence of various adverse events, including digestive (diarrhea and poor appetite), neurological (headache and tinnitus), and distress-related (tenseness, worrisome, and irritation) symptoms. A large body of evidence suggests the benefits of acupuncture regimens in the management of therapy-related adverse events in breast cancer patients (Chao et al., 2009). Acupuncture has been recommended for reducing chemotherapy-induced nausea and vomiting during and after breast cancer treatment (Greenlee et al., 2017). It is also effective for treating episodic and chronic tension-type headaches (Nielsen, 2017), tinnitus (Liu et al, 2016), anxiety and stress-related symptoms (Amorim et al., 2018). This study provides additional evidence supporting our assumption that EA/TNS + BA is not only effective in preventing chemotherapy-associated cognitive impairment, but also beneficial in reducing related side effects, in particular digestive, certain neurological, and stress-related

Table 5
Incidences associated with breast cancer and chemotherapy, n (%).[a]

Event[b,c]	Baseline			Week 4			Week 8		
	EA/TNS + BA	MAS	P^a	EA/TNS + BA	MAS	P^a	EA/TNS + BA	MAS	P^a
Diarrhea	7 (15.5)	9 (19.1)	0.858	2 (4.4)	10 (21.3)	**0.037**	1 (2.2)	5 (10.6)	0.226
Tenseness	14 (31.1)	16 (34.0)	0.938	3 (6.7)	12 (25.5)	**0.030**	7 (15.6)	8 (17.0)	0.927
Worrisome	16 (35.6)	17 (36.2)	0.876	5 (11.1)	16 (34.0)	**0.018**	11 (24.4)	13 (27.7)	0.910
Irritation	12 (26.7)	13 (27.7)	0.899	4 (8.9)	13 (27.7)	**0.040**	6 (13.3)	14 (29.8)	0.108
Headache	6 (13.3)	11 (23.4)	0.329	3 (6.7)	10 (21.3)	0.087	1 (2.2)	8 (17.0)	**0.042**
My family has accepted my illness	40 (88.9)	32 (68.1)	**0.030**	38 (84.4)	27 (57.4)	**0.009**	37 (82.2)	30 (63.8)	0.080
I am satisfied with how I am coping with my illness	23 (51.1)	26 (55.3)	0.845	26 (57.8)	14 (29.8)	**0.013**	23 (51.1)	19 (40.4)	0.413
I have difficulty eating rich or "heavy" foods	14 (31.1)	5 (10.6)	**0.030**	3 (6.7)	6 (12.8)	0.526	7 (15.6)	8 (17.0)	0.927
I get a ringing or buzzing in my ears	2 (4.4)	2 (4.3)	0.641	0	3 (6.4)	0.256	0	6 (12.8)	**0.026**

[a]Data were examined using Chi-square (χ^2) or Fisher Exact test. Those which statistical differences reached significance level are indicated in bold font. EA/TNS + BA, electroacupuncture trigeminal nerve stimulation plus body acupuncture; MAS, Minimum Acupuncture Stimulation.
[b]The items listed herein were extracted from EORTC QLQ-C30 and BR23 (V3), Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B), Functional Assessment of Chronic Illness Therapy (FACIT), Functional Assessment of Anorexia/Cachexia Therapy (FAACT), Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane), and Functional Assessment of Cancer Therapy-Biologic Response Modifier (FACT-BRM).
[c]The items listed herein are those which were rated as "3" (quite a bit) or higher and incidences were significantly different between EA/TNS + BA and MAS in any assessment point.

symptoms.

In this study, we found that the EA/TNS + BA group achieved better social/family function and emotional wellbeing during the course of treatment, reflected in more EA/TNS + BA-treated patients who were satisfied with how they were dealing with their illness and whose family had accepted their illness at Week 4. The better outcomes achieved are most likely due to the EA/TNS + BA's improvement in stress-related symptoms, including tenseness, worrisome, and irritation. Given that cancer-related distress and anxiety are closely associated with poorer treatment outcomes and poorer quality life in cancer population (McMullen et al., 2018), this study suggests that EA/TNS + BA could improve the quality of life by increasing the ability to manage cancer-related distress.

The broad effects observed in this study appear to be related to acupuncture regimen used. Unlike previous studies in which most acupoints used for the treatment of cancer patients are located on the body and generally stimulated only with manual manipulation (Chou et al., 2009; Guo et al., 2002; Yu et al., 2006; Zhao et al., 2009; Zhou and Jin, 2008), this study utilized a combination of dense forehead and body acupoints and electrical stimulation was further conducted on forehead acupoints. The forehead acupoints are innervated by the trigeminal sensory pathway that has more intimate collateral connections with the brainstem reticular formation, particularly the raphe nuclei containing serotonin (5-HT)-producing neurons (Arbab et al., 1988; Kubota et al., 1988) and the locus coeruleus containing noradrenaline (NA)-producing neurons (Simpson et al., 1999; Takahashi et al., 2010). The brainstem 5-HT and NA neuronal systems play a pivotal role in acupuncture modulation of multiple brain functions, including the processing of pain, mood, and cognition information (Dhond et al., 2007; Zhao, 2008). The addition of electrical stimulation and body acupuncture could enhance neuromodulatory effects of acupuncture (Dhond et al., 2007; Qu et al., 2013). This notion is confirmed by our previous studies that have demonstrated a rapid antidepressant effect of EA/TNS on forehead acupoints (Zhang et al., 2012) and a long-lasting enhancement of the antidepressant effects of EA (Qu et al., 2013) in the treatment of major depressive disorder. Transcutaneous electrical stimulation on V1 trigeminal branches-innervated forehead also has significant effects in reducing epilepsy, depression and ADHD (Cook et al., 2016; DeGiorgio et al., 2013; McGough et al., 2019; Schrader et al., 2011). It thus appears that a combination of EA/TNS and body acupuncture particularly with electrical stimulation on forehead acupoints could produce prolonged additive and even synergistic effects by broadly modulating neurochemical pathways and brain regions.

The superior efficacy of EA/TNS + BA may also be attributed to acupuncture control mode and the number of acupoints used. In this study, the choice of MAS as control was based on neuroimaging findings that the more widespread and intense effects of acupuncture in modulating brain regions are associated with more efficient and effective acupuncture stimulation (Zhang et al., 2012b). This suggests that the optimal control for brain effects of acupuncture should be kept at the minimum level in both quantity and quality of acupuncture stimulation. In addition, compared to other acupuncture control procedures, MAS is more practicable and better maintenance of blinding (Hammerschlag, 1998). This has been validated in our recent study (Zhang et al., 2020). On the other hand, there were total 27 acupoints used in this study, many more than most previous similar studies (Chou et al., 2009; Guo et al., 2002; Yu et al., 2006; Zhao et al., 2009; Zhou and Jin, 2008). Inadequacy of acupuncture stimulation is thought to be an important factor associated with negative results of acupuncture trials (Zhang et al., 2012b).

Several limitations of this study should be considered. Firstly, this study failed to detect a statistically significant difference in MoCA and prevalence of chemobrain between the two groups. This seems to be largely due to subtle cognitive deterioration which the overall MoCA could not detect. Whether prolonged treatment duration could produce significant differences for MoCA deserves for further investigation. Secondly, although assessors and participants were blinded to treatment, and the credibility assessment indicated a high successfulness of blinding, with a JBI value of 0.79 (95% CI: 0.72 to 0.87), acupuncturists were not blinded to treatment. Bias from acupuncturists could not be completely excluded (Witt et al., 2012). Thirdly, similar to most previous studies (Zhang et al., 2010), the determination of body acupoints used in this study was basically based on empirical evidence. Empirical treatment regimens have resulted in a large variation in acupuncture protocols and difficulties in comparing treatment outcomes among trials. Finally, cognitive performance was measured only with MoCA and digit span test in the current study. Other scales, such as auditory verbal learning test, shape trails test, animal fluency test, Boston naming test, should be included to examine other cognitive domains in the future. In addition, no biomedical approaches, such as neuroimaging brain function, were included in the measurement of treatment outcomes. Our recent several studies have demonstrated close associations of chemobrain with microglia-mediated cytokines, neuroinflammation, and neuroplasticity in animal models (Shi et al., 2018, 2019a,b). Further exploration of the underlying mechanisms of acupuncture effects would help develop more effective interventions for chemobrain.

In summary, EA/TNS + BA may be particularly beneficial in reducing chemotherapy-induced working memory impairment and the incidence of certain digestive, neurological, and distress-related symptoms. It could serve as an effective intervention for breast cancer patients under and post chemotherapy.

5. Authors' contributions

ZZJ, RCYL, KWSC, AV, and YYD were involved in conception, design of the study, and critical comments on the manuscript. ZZJ and LMH conducted data analysis. ZSQ and YYD conducted re-examination and re-analysis of the data set. ZZJ drafted the manuscript. SCM performed clinical assessment and collected data. LLY and CYY carried out acupuncture treatment. VHFL, WFY, and WKS provided critical comments.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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