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Acupuncture and the relaxation response for treating gastrointestinal symptoms in HIV patients on highly active antiretroviral therapy

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Abstract

Objectives—To examine the effect of acupuncture and the relaxation response (RR) for treating gastrointestinal (GI) symptoms in HIV patients who are using highly active antiretroviral therapy (HAART).

Methods—The authors conducted a 4-arm 2×2 double-blind randomised controlled trial in an acupuncture clinic in the USA. Sham acupuncture and health education were used as the control conditions of real acupuncture and RR elicitation, respectively. Enrolled patients were randomised to real acupuncture+RR (AR), sham acupuncture+RR (SR), real acupuncture+health education (AE) or sham acupuncture+health education (SE) study arm. Participants listened to CDs with RR-eliciting instructions or health education while receiving acupuncture intervention. Interventions were provided twice weekly for 4 weeks and once weekly for another 4 weeks. Participants used daily diaries to record GI symptom severity ratings (0–10). The authors estimated the intervention effect as the changes in symptom rating per intervention session increase using a mixed-effects regression model.

Results—A total of 130 people with HIV/AIDS who were on HAART and had persistent GI symptoms were enrolled and 115 started the study intervention. The AR group had greater intervention effects for loose stools symptoms than the other three groups ($\beta=-0.149$, -0.151 and -0.144 , p value=0.013, 0.013 and 0.018 comparing AR to AE, SR and SE, respectively). The AR group also had significant intervention effects on reducing nausea symptoms when the intervention was given twice per week ($\beta=-0.218$, $p=0.001$).

Conclusions—Our trial provided preliminary data demonstrating the potential synergistic effects of acupuncture and RR for treating GI symptoms in HIV patients on HAART.

INTRODUCTION

Gastrointestinal (GI) symptoms are highly prevalent among people with HIV/AIDS (PWA).^{1–4} GI side effects were also among the most frequently reported complaints related to the use of highly active antiretroviral therapy (HAART)⁵ as well as newer improved

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regimens.^{6–8} GI toxicity has been reported as one main reason for medication discontinuation.^{9–13} High medication adherence rates remain essential for optimal treatment effects and are recommended for all antiretroviral regimens.¹⁴ Although HAART provides PLWA with the chance of living longer and healthier lives, the life-long need for consistently high levels of medication adherence highlights the need to identify non-pharmacological interventions for treating GI side effects.

Acupuncture has been shown to be effective in managing GI side effects of cancer chemotherapy^{15–17} and following surgical anaesthesia.^{18–22} Several descriptive studies have indicated that PLWA use acupuncture and gain benefit from it to address a variety of GI symptoms.^{23–25} A small pre-post intervention study showed that acupuncture improved stool frequency and consistency among PLWA who suffered from chronic diarrhoea.²⁶ Rigorous randomised controlled trials that examine the effects of acupuncture in controlling GI symptoms among PLWA are, however, still needed.

One feature of acupuncture treatment is the induction of calm and deep relaxation in mind and body.²⁷ This feature is shared by a commonly used mind/body practice, the relaxation response (RR) elicitation. The RR is a physiological state that has the opposite effect of the fight-or-flight response.²⁸ The shared features of these two therapies can complement each other in that acupuncture facilitates the effect of RR and, on the other hand, RR prepares the body to be more responsive to acupuncture. Although the way in which acupuncture and the RR exert their effects is not well understood and remains an area of on-going scientific enquiry, studies have found similar physiological and neurological responses produced by these two therapies such as the release of opioid neurotransmitter and nitric oxide.^{29–33} There is, however, a fundamental difference between these two modalities. The acupuncture treatment requires a practitioner, namely an acupuncturist, whereas the RR is a self-care approach. Given their similarities and differences, it is of great interest to study the effect of these two regimens by comparing their individual effects as well as estimating the combined effects. Because individuals receiving acupuncture often listen to relaxing music or sounds of nature during their treatments, our study findings on the combined effects of acupuncture and the RR can have clinical implications for acupuncture practice.

Currently, the knowledge of optimal dosage of acupuncture and mind/body techniques for treating patients of any disease and condition is lacking.³⁴ Establishing a dose–response relationship is the first step for obtaining the optimal dosage.³⁵ Unlike pharmaceutical research, which has a well-established definition of drug dosages, there is no uniform measure of dosage for acupuncture or mind/body interventions. In the literature, number of acupuncture needles, treatment frequency, duration of treatment sessions and number of treatment sessions have been used as measures of acupuncture dosage.^{35, 36} Number of treatment sessions has also been used to measure the dosage of a cognitive behavioural intervention.³⁷

In this study, we examined the effect of acupuncture alone, the RR alone and the combination of the two on reducing GI symptoms among PLWA. We also examined whether the frequency of the treatment affects the intervention effect, as a way to evaluate the dose–response effects.

METHODS

Study design

We conducted a 4-arm (2×2) double-blind randomised controlled trial with two study interventions, acupuncture and the RR, and used sham acupuncture and health education as controls for each of the interventions. Patients were randomly assigned to one of the four

study groups: acupuncture + RR (AR), acupuncture + health education (AE), sham acupuncture + RR (SR) or sham acupuncture + health education (SE). Study subjects received 8 weeks of acupuncture (real or sham) for 30 min twice per week for the first 4 weeks and once per week for the following 4 weeks. While receiving the acupuncture (real or sham) intervention, the study subjects wore ear buds to listen to a RR-eliciting CD or a health education CD according to their group assignment. The study was reviewed and approved by the Institutional Review Board (IRB) of the Boston University Medical Center and the VA Boston Healthcare System, as well as the New England IRB, which oversees the research of Pathway to Wellness where the study was conducted.

Randomisation and blinding

We used a block randomisation method with block size of 8, stratified by gender. A series of random numbers was generated in advance using a computer program and each number was placed in an individual sealed, opaque envelope. Following completion of the baseline outcome measures, a research assistant (RA) opened the next envelope in the predetermined sequence to assign a study group to the participant. Only this RA was aware of the patient group assignment. The acupuncturists were aware of the acupuncture intervention assignment, but not the CD assignment because the study subjects wore ear buds to listen to the CD. Remaining study personnel including the RAs who collected the study data were blind to subjects' group assignments. In addition, for blinding purposes, the study participants were told that the purpose of the study was to evaluate the effect of acupuncture techniques along with various health management CDs in helping them manage their GI symptoms. We also instructed the study participants not to discuss the contents of the CD with anyone.

Patient population

The study sample included patients diagnosed as HIV-positive who had at least one of six GI symptoms: diarrhoea, loose stools, gas/bloating, abdominal pain, nausea and vomiting for at least 8 weeks. These symptoms were chosen for their high prevalence among PLWA, and are also included in the standardised symptom checklist used in this study that specifically includes these six symptoms. Patients were also required to have been on a stable antiviral regimen (nucleoside/nucleotide reverse transcriptase inhibitor (NRTI/NtRTI), non-nucleosides (NNRTIs) or protease inhibitor (PI)) for at least 8 weeks. Patients were ineligible if they reported having (1) current major opportunistic infections or medical complications that might require hospitalisation and additional pharmaceutical intervention, (2) GI conditions not related to their HIV diagnosis and the side effects of HAART or (3) haemophilia or other bleeding disorders. These inclusion and exclusion criteria ensured that the GI symptoms were likely to be related to use of HAART. Other exclusion criteria included being pregnant; current use of acupuncture for treating GI symptoms; currently practicing RR-eliciting techniques, such as yoga or meditation; current enrolment in another clinical intervention study; or cognitive impairment as measured by the Mini-Mental Status Examination, with a score of lower than 24.^{38, 39}

Patients were first screened briefly through a phone interview followed by an in-person full screening (see figure 1 for the recruitment flowchart and statistics). All the enrolled patients signed an informed consent form.

Study intervention

Acupuncture intervention—The study participants received a total of 12 treatments in the 8-week intervention period. Patients in the two real acupuncture groups (AR and AE) received acupuncture needle insertion on the following GI symptom-specific points: PC6 (Neiguan), CV12 (Zhongwan), ST37 (Shangjuxu) and Auricular Spleen point. These points

were chosen in accordance with Chinese medicine practice principles in addition to being based on previous study results^{15–17, 40} and our clinical experience. Three of these points are bilateral (PC6, ST37, Auricular Spleen) and CV12 is unilateral located on the front midline of the thorax. As such, these four points collectively can address the entire constellation of GI symptoms commonly reported. We used Seirin needles gauges 2 and 3 for body points and Seirin gauge 1 for ear points. Needle insertion for all points used in the study was done according to standard procedures of clean-needle technique using sterile, disposable needles. Needles were inserted to a depth required to elicit the *de qi* with mild stimulation and retained for 30 min with the participant resting comfortably on a treatment table.

We chose the following acupuncture points as the comparison points for use in the two sham acupuncture groups (SR and SE): TE4 (Yangchi), CV21 (Xuanji), BL59 (Fuyang) and Auricular Shoulder point. TE4, BL59 and Auricular Shoulder points are bilateral. These points were chosen because of their close proximity to each of the symptom-specific points as well as their lack of therapeutic effect on digestive function according to the literature on Traditional Chinese Medicine^{40, 41} and our previous pilot study results.⁴²

To further minimise the possible physiological effect from needle insertion and stimulation, the study acupuncturists placed an electrode pad on each comparison point which was then attached to a cable connected to a decommissioned electrical stimulator unit. This is a well-validated placebo acupuncture technique^{43–45} and its credibility has been shown to be the same as real acupuncture treatment by study participants in a randomised acupuncture trial.⁴⁶ To further ensure that participants did not question the credibility of this method of acupuncture treatment, research staff told participants that the study was comparing two types of intervention: (1) acupuncture with needles and (2) treatment with a machine designed to stimulate acupuncture points through skin electrodes.

RR intervention—The RR intervention was implemented while participants were receiving acupuncture intervention. Subjects listened to CDs with small ear buds to mask content of the CDs from the acupuncturist. The CDs were labelled in such a way that only the RA who assembled the CDs for each study participant could identify the content of each CD. Such a design is used to blind the acupuncturist to participants' CD assignments. Participants in the AR and SR groups listened to CDs with the instructions to elicit the RR; the other two study groups (AE and SE) had CDs that contained health education information.

Six different techniques for eliciting the RR were provided to participants: (1) breathing awareness, (2) mental repetition of a word, sound, phrase or prayer, (3) autogenic – self hypnosis, (4) progressive muscle relaxation, (5) guided body scan and (6) guided imagery. These six techniques are commonly used for eliciting the RR and were used in our previous studies on patients with chronic heart failure and HIV.^{47, 48} In addition to listening to the CDs during their acupuncture intervention sessions, all participants in the AR and SR groups were also asked to listen to these RR-eliciting CDs at home once a day during the 8-week study intervention period. The availability of more than one technique allows for individuals' preferences for certain techniques and avoids overuse of a single technique, which may interfere with participants' willingness to practice at home.

Twelve 20-min CDs containing different topics of health education information were used as the control to the RR CDs during the 12-session study intervention period. Another 56, 20-min health education CDs were used for daily home practice during the 8-week study intervention period. The health education CDs included information about management of HIV-related symptoms, nutrition, Chinese Medicine, Mind-Body-Spirit connection and

various self-help topics such as positive thinking, optimism and emotional intelligence. These health education CDs did not contain any RR-eliciting instructions.

Study measures

We used the GI symptom subscale of the Revised HIV Sign and Symptom Checklist (SSC-HIV) to measure the intensity of the six targeted GI symptoms: diarrhoea, loose stools, gas/bloating, abdominal pain, nausea and vomiting. The SSC-HIV is a standardised validated scale, which was first developed in 1999 and then revised in 2001.^{49, 50} The reliability estimates of the subscales in the revised version range from 0.76 to 0.91, and the estimate is 0.89 for the GI symptom subscale.^{49, 50} Study participants were asked to rate the severity (0–10 with 0 indicating no symptom and 10 most severe level of the symptom) of each of the six GI symptoms daily using a study diary.

Although we requested that participants not use anti-diarrhoea, anti-emetic or anti-nausea medications to treat their GI symptoms during the study period, we asked them to record the usage if they did use them. Use of these medications was included as a potential confounding factor in the analysis.

Statistical analysis

We estimated the change in the GI symptom severity rating per treatment session by fitting a mixed (fixed and random) effects regression model. In the regression model, the fixed effect independent variables included 'number of intervention sessions', 'group indicator variables of AE, SR and SE groups, as such AR group was used as the reference group' and 'the interaction terms of number of intervention sessions and group indicator variables'. A random effect independent variable was used to capture the correlation among repeated measures obtained from the same patient. The regression coefficient (slope) of the independent variable 'number of intervention sessions' indicates the rate of symptom severity changes for the AR group (reference group). The symptom change rates of AE, SR and SE groups can also be derived from the regression coefficients in the model. A significant negative change rate (ie, symptom reduction) will support the intervention effect. The regression coefficients of the interaction terms indicate the group difference in the change rate.

We first fitted a one-slope regression model, which assumed a constant change rate across the 12 sessions of intervention (two sessions per week for the first 4 weeks and then once per week for the following 4 weeks) for each group. We then fitted a two-slope regression model to estimate the change rate for the first 4 weeks (first slope) and the following 4 weeks (second slope) separately. This two-slope regression model was used to examine the intervention effect of twice per week versus once per week intervention sessions. Finally, we included the use of anti-diarrhoea medications in the regression model to adjust for possible confounding effects.

We employed an intent-to-treat analysis by including all available data for analysis, that is, including all data collected from the weekly study diaries of all enrolled subjects regardless of whether they completed the study (figure 1). We further adjusted for potential biases from missing data using a model-based approach by controlling for factors such as baseline rating that may be associated with the missingness in the regression model.^{51, 52} The PROC MIXED procedure in SAS was used for analysis.⁵³

RESULTS

Study participant characteristics

Between April 2007 and July 2009, we enrolled 130 participants and 115 of them started the study intervention (figure 1). The study sample consisted of 115 subjects (31 in AR, 27 in AE, 27 in SR and 30 in SE) ranging from 25 to 68 years of age with a mean age of 46.6 years; 70% of them were male, 31% white, 46% African American, 17% Hispanic and 6% other races. There was no group differences in age, gender or race. The four study groups also had similar CD4 counts (overall mean 522, median 481 and SD 291) and viral loads (88% with undetectable values) at the baseline. There were similar percentages of patients in the four groups who were taking each type of HAART. All but two patients were on NRTIs, on average 15% were on NNRTIs and 67% on PIs. Approximately 10% of the study participants reported using anti-diarrhoea medications during the study period, and there was no group difference in the usage.

Dropout bias assessment

Eighty-nine (25 in AR, 20 in AE, 21 in SR and 23 in SE) of the 115 subjects completed the 8-week study intervention. There was no group difference in the dropout rate. The main reason (62%) for dropout was 'lost to follow-up' after many attempts to reach participants by either phone or mail. This was related to the fact that many of the study participants were living in temporary housing such as homeless shelters. The next most common reason for dropout (17%) was 'no time to attend the study intervention sessions'. There was a trend showing that those who did not complete the study intervention had a slightly higher symptom severity rating at baseline, although not statistically significant. We therefore controlled for the baseline rating when estimating the intervention effects.

Intervention effects

The results from the mixed-effects regression model showed that all four study groups had significant intervention effects during the 8-week study intervention in reducing the symptom of loose stools as indicated by the negative regression coefficients (table 1). More strikingly, the AR group had a greater effect than each of the other three groups as indicated by the significant differences in the regression coefficients ($\beta = -0.149, -0.151$ and -0.144 , p value = 0.013, 0.013 and 0.018 comparing AR to AE, SR and SE, respectively). That is, the AR group had a greater decrease in the symptom rating per intervention session increase as compared to the other three groups. The intervention effect was not significantly different among the three groups: AE, SR and SE. When examining the intervention effect during the first 4 weeks and the following 4 weeks of study intervention period separately, the results from a two-slope regression model indicated that the AR group had a significant intervention effect during the first 4 weeks ($\beta = -0.239$, $p < 0.0001$, figure 2) as well as during the following 4 weeks ($\beta = -0.208$, $p = 0.04$, figure 2) of the study intervention period. The other three groups had a significant intervention effect during the first 4 weeks of intervention ($\beta = -0.092, -0.089, -0.086$; $p = 0.041, 0.052, 0.063$ for AE, SR and SE, respectively), but not during the following 4 weeks of intervention. The results remained the same after controlling for the use of anti-diarrhoea medication.

For the nausea symptom, the AR group demonstrated a greater intervention effect with borderline significance than the other three groups combined (slope difference = -0.120 , $p = 0.099$) during the 8-week intervention period (table 1). The results of the two-slope regression model indicated that the significant intervention effects in the AR group were from the first 4-week intervention period ($\beta = -0.218$, $p = 0.001$, figure 3). The intervention effects were not statistically significant during the second 4-week intervention period ($\beta = -0.125$, $p = 0.19$, figure 3). For the other three groups, the intervention effects for reducing

nausea symptoms were not significant either during the first 4-week or the second 4-week intervention periods.

All four study groups showed significant intervention effects on reducing diarrhoea and gas/bloating, and there was no significant group difference in the effect. There was also no significant group difference in the effects of reducing symptoms of abdominal pain and vomiting.

Adverse effects

There were no adverse events reported during the study period that were related to the study intervention.

DISCUSSION

Our study provides rich data on daily symptom ratings that allowed us to estimate the intervention effect per treatment session increase of acupuncture and the RR for treating GI symptoms. The results indicate that as the number of intervention sessions of the combination of acupuncture and the RR treatments increases, the greater the reduction in symptoms of loose stools and nausea. The interventions of acupuncture and the RR were more effective when used in combination than when used alone. These results demonstrate the possible synergistic effects of combining acupuncture and the RR for treating two common side effects of HAART – loose stools and nausea.

The data show that all four study groups had significant effects in reducing the diarrhoea symptom and no group difference was observed. Because the symptoms of diarrhoea and loose stools might appear similar to study participants and they may not have distinguished the two symptoms in the same way, we conducted an ad hoc analysis by creating a variable that was the higher value of the two symptom ratings of diarrhoea and loose stools. The results indicate that the AR group had a greater intervention effect than the other three groups combined ($\beta = -0.137$, $p = 0.011$) in this diarrhoea/loose stools combination symptom rating variable. The intervention effects were significant both with twice per week AR combination intervention or once per week intervention.

Although not a perfect design for a dose–response effect analysis, our study shed some light on the effect of treatment frequency. The data suggest that twice per week treatments might be more effective than once per week treatments for addressing GI symptoms. Future randomised clinical trials that are specifically designed to evaluate the effects of various dosages and frequency of complementary and alternative medicine (CAM) therapies are needed to further examine these factors.

Our study findings, if validated in future larger studies, can have important implications in providing CAM therapies to HIV-positive patients for managing HAART GI side effects. This study replicated our previous study in demonstrating the feasibility of combining acupuncture and the RR in a clinical setting.^{47, 54} In addition, integrating the RR into an acupuncture clinic fits the natural style of practice. Ultimately, the provision of two non-pharmaceutical modalities that can augment each other, with one that involves a self-care approach, may optimise HAART treatment outcomes and potentially be cost-effective.

This study has a number of strengths: (1) the double-blind study design controlled for non-specific effects such as expectation for improvement from being assigned to an intervention group and potential biases from the research staff who collected data and (2) the use of sham acupuncture and health education as control conditions to real acupuncture and the RR further controlled for potential placebo effects. The study participants in all four study

groups rated the intervention they received to be highly credible using a credibility scale for acupuncture study.⁵⁵

There are some limitations to this study. First, data on symptom severity were self-reported. Second, the study was conducted in a acupuncture clinic in Boston, MA, USA, where CAM modalities are well-accepted and commonly practiced. The implication of the study findings might not be generalisable to other clinics in other areas of the USA or the other parts of the world. Third, the dose-response analysis was based on twice per week followed by once per week treatments on the same patients. Some factors, such as treatment order and treatment threshold/ceiling effects, might have affected the results.

In conclusion, our data demonstrate the likely combined effects of acupuncture and the RR in treating persistent GI symptoms among patients who are on stable antiretroviral medication treatments. Furthermore, the intervention effects seem to be affected by the frequency of treatment. Our study provides preliminary evidence that can be used as a foundation for further investigation of the synergistic effects of these two commonly used CAM modalities.

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Summary points

- Gastrointestinal symptoms are common in people living with HIV/AIDS
- We conducted a 4-arm study of acupuncture, relaxation, and two controls
- The combination of acupuncture and relaxation had a significantly greater effect

Figure 1.
Recruitment and intervention flowchart.

Figure 2. Loose stools symptom ratings by number of intervention sessions received: predicted from a two-slope regression model controlling for baseline ratings.

Figure 3. Nausea symptom ratings by number of intervention sessions received: predicted from a two-slope regression model controlling for baseline rating.

Table 1

Intervention effects: regression slopes β estimated from the one-slope mixed-effects regression model controlling for baseline ratings

Symptoms	Study group					
	AR		AE		SR	
	β^*	p Value	β	p Value	β	p Value
Diarrhoea	-0.18	0.001	-0.11	0.02	-0.10	0.04
Loose stools	-0.24	<0.0001	-0.09	0.05	-0.08	0.05
Gas/bloating	-0.11	0.03	-0.10	0.06	-0.12	0.02
Abdominal pain	-0.09	0.13	-0.14	0.02	-0.03	0.58
Nausea	-0.21	0.002	-0.06	0.35	-0.10	0.16
Vomiting	-0.05	0.12	-0.03	0.38	-0.03	0.37

AR, acupuncture + relaxation response; AE, acupuncture + health education; SR, sham acupuncture + relaxation response; SE, sham acupuncture + health education.

*. Regression coefficient of the fixed effect independent variable 'number of intervention sessions' in the mixed-effects regression model. The dependent variable is the symptom severity rating (0–10).