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The Effects of Acupuncture on Insomnia, Anxiety, and Depression in Women with Chronic Liver Disease: A Randomized Controlled Trial

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Abstract

Objective: To evaluate the feasibility and effects of acupuncture on insomnia, anxiety, and depression in women with Chronic Liver Disease.

Patients and Methods: Twenty-four women patients over the age of 18 years who had liver disease complicated by psychiatric disorders such as insomnia, anxiety, and depression were randomly assigned to either the treatment group (n=12) or the control group (n=12). In the treatment group, acupuncture was performed 3 times per week for 4 weeks (12 sessions in total). In control group, there was no acupuncture but the same assessment with treatment group. Insomnia, anxiety, and depression were measured using the National Cancer Center (NCC) scoring system. We assessed deterioration of liver disease using the Child score and blood tests.

Results: In the treatment group, the mean NCC insomnia, anxiety, and depression scores decreased significantly over the treatment period; control group scores did not decrease significantly. After 12 acupuncture treatments, the total NCC score for insomnia, anxiety, and depression was significantly lower in the treatment group compared with that of the control group. After the trial, liver function of neither group got worse.

Conclusions: These results suggest that acupuncture treatment may be beneficial in improving insomnia, anxiety, and depression among patients with chronic liver disease without worsening of liver function. Further study with a larger sample size including male participants is needed to confirm our findings.

Keywords: Acupuncture; Insomnia; Anxiety; Depression; Chronic liver disease

Introduction

Liver cirrhosis associated with chronic hepatitis [1-4]. and hepatocellular carcinoma (HCC) [5] has been reported to cause psychiatric problems. Chronic liver disease is associated with impaired health-related quality of life (HRQOL), depression, anxiety, and other psychological impairments [6,7]. In cases where these chronic conditions stigmatize the patient, psychological impairment becomes more pronounced. Moreover, complications of advanced liver disease may be associated with poorer HRQOL irrespective of the cause of the liver involvement. These psychiatric disorders have been attributed to the production of toxic metabolites that damage the brain, resulting in neurological and psychological problems [8].

In general, doctors should avoid prescribing long-term use of drugs for the treatment of psychiatric disorders, as it could further deteriorate liver function in patients with liver disease [8]. For instance, antidepressant drugs have been reported to be associated with several adverse drug reactions including hepatotoxicity [9]. Nevertheless, long-term use of anti-anxiety and anti-depressant drugs may be necessary, which paradoxically may exacerbate the condition [10].

Some studies suggested that acupuncture had the potential to treat psychological disorders including anxiety, insomnia, and depression [11-14]. Despite the large number of studies on this subject, few addressed the use of acupuncture to treat psychiatric problems associated with chronic liver disease. A few articles reported that acupuncture alleviated depression related to chronic hepatitis or otherwise impaired liver function. One observational study showed the improvement of depression after acupuncture in 28 patients with chronic hepatitis [7,15,16]. There were acupuncture studies with negative turnover of hepatitis B virus versus control group via examination of physiological parameters [14,15].

In our previous pilot study, acupuncture resulted in significant improvements in insomnia, anxiety, and depression in HCC patients with liver cirrhosis. Moreover, there was no worsening signs of liver function after treatment and adverse events did not occur during the trial [17].

This randomized controlled trial was parallel design and allocation ratio was 50%. This study aimed to reconfirm previous findings and establish the clinical effects of acupuncture for the alleviation of insomnia, anxiety, and depression in patients with chronic liver

disease such as HCC, liver cirrhosis, and chronic hepatitis. For the evaluation of acupuncture safety, we also examined the changes of blood composition of patients.

Materials and Methods

Ethics statement

This trial was approved by the Institutional Review Board of Daegu Catholic University Hospital, and was conducted in accordance with the provisions of Declaration of Helsinki (1989) and Good Clinical Practice (GCP). It was registered on Clinical Research Information Service (KCT0001411) retrospectively. The reason for non-registration before participants recruitment was that this regulation for registration had not been strongly recommended in 2012.

Participant recruitment

Twenty-four participants were enrolled in the clinical trial between September 7, 2012 and March 16, 2013. Participants were informed of the purpose, method, anticipated adverse dangers and discomforts, disclosure of personal information, compensation, and right to discontinue the clinical trial. All patients signed an agreement to participate at one's own will. This study was approved by the Institutional Review Board of Daegu Catholic University Hospital. Participants were recruited via a recruitment notice on the web site or a poster. The required sample size was estimated to be a total 24 participants, considering a drop-out rate of 20%.

Inclusion and exclusion criteria

The subjects were female patients, over 18 years of age, diagnosed with chronic liver disease such as HCC, liver cirrhosis, and chronic hepatitis. In addition, inclusion criteria were complaints of distress with a National Cancer Center (NCC) psychological symptoms score higher than 4 points in both severity and inconvenience in one at least one of the following: anxiety, depression, or insomnia.

Other inclusion criteria included, a Child-Pugh score, a scoring system used to assess the severity and prognosis of chronic liver disease and cirrhosis, lower than 9 in classification either A or B, serum bilirubin level of 5 mg/dL or lower, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values of 100 IU/L or lower, serum creatinine value of 1.5 mg/dL or lower, and an INR) of 2.0 or lower.

The subjects underwent a washout period 3 days before the trial, in which the administration of tranquilizers and antidepressants was limited. The subjects were required to be monitored during the trial and to follow the restriction standards of the trial.

The exclusion criteria included severe neutropenia (absolute neutrophil level of 500/uL or lower), platelet count less than 50,000/uL, fever, aggravation of liver function, abdominal aneurysm, sepsis, and thrombosis. Pregnant women (positive human chorionic gonadotropin) and subjects judged by investigators to have difficulty continuing the trial were also excluded.

Intervention

In treatment group, a total of 12 sessions of acupuncture was performed, 3 sessions per week for 4 weeks. Acupuncture points, Neiguan (PC6), Gongsun (SP4), Shenmen (HT7), Yintang (EX-HN3), Hegu (LI4), Taichong (LR3) and Baihui (GV20) were applied in the treatment group to a total of 9 acupuncture points including bilateral LI4 and LR3. Stainless steel needles (0.20 × 30 mm; Dongbang acupuncture, Korea) were used and retained for 25 minutes after insertion. Acupuncture was performed by a traditional Korean medicine (TKM) physician who was registered and had at least 3 years of clinical experience. Acupuncture was manually performed with a sensation of de qi. In Control group, no acupuncture or placebo was conducted, but the same assessment with treatment group was performed.

Outcome measurements

The effects of acupuncture were assessed using the NCC scoring system for psychological symptoms. The NCC scoring system questionnaire consists of 2 questions each for the 3 symptoms of insomnia, anxiety, and depression. Question 1 inquired about the severity of the symptom, and Question 2 inquired about the inconvenience caused by one of the symptoms. Each question included a scale of 0 [none] to 10 [extremely severe], a higher score meaning greater severity and inconvenience [18].

Measurement taken at 3 points over 4 weeks included baseline, midtreatment (2weeks after initiation), and end of treatment (4 weeks after initiation). Patients were assessed through physical examination (body temperature, blood pressure, pulse, body weight), Child-Pugh score and laboratory examination, and NCC psychological symptoms scores.

Safety evaluation

To evaluate the safety of acupuncture, the body temperature, blood pressure, pulse, and body weight of the participant were assessed at each visit. Child-Pugh scores and biochemistry tests (AST, ALT, BUN, Creatinine, T-bilirubin, Albumin, prothrombin time (PT)) were performed at 0, 2, and 4 weeks for patients in the treatment and control groups. Adverse events were examined by the investigator at each visit.

To check for aggravation of liver cirrhosis, patients were evaluated for hepatic coma, hepatorenal syndrome, hemorrhage from rupture of esophageal and gastric varices, infection/sepsis, spontaneous peritonitis, and liver function failure. For patients with aggravated liver cirrhosis, the investigator decided whether to discontinue the trial and hospitalization.

Compliance was calculated from the attendance rate of more than 80%, and any participant absent for 5 consecutive appointments was regarded as a drop-out. Participants were told to immediately report any adverse events between visits. Any abnormal condition following acupuncture was to be investigated in relation to the clinical trial and followed up.

Sample size determination

Sample size was determined based on a preliminary study [17] where the difference value of NCC total score average of patients between acupuncture group and control group with mean was 9.630 and standard deviation was 7.518 is considered to be of clinical relevance. To detect this difference, we need a sample size of 10 in each group (α=0.05, β=0.20). To allow 20% for drop to follow up, our proposed trial requires 24 patients (12 for each group).

Statistical analysis

The data was analyzed using intention-to-treat approaches. Statistical analyses were carried out using the program PASW (new version of SPSS Win Ver.) 19.0. Two sample t-test and chi-square test were used to compare between treatment and control group for baseline characteristics. Repeated measure 2-factor analysis was used to analyze change of total NCC scores according to time and group and contrast was used to analyze the multiple comparison result. At last, the result was regarded as statistically significance when p-value less than 0.05.

Results

Baseline characteristics

Of the 24 women outpatients were screened and randomly assigned to the acupuncture (n=12) and control groups (n=12). There was no difference in baseline characteristics between treatment and control group except for number of cirrhotic patients (Table 1). Twenty-one patients completed the trial with drop-outs of 3 patients (Figure 1).

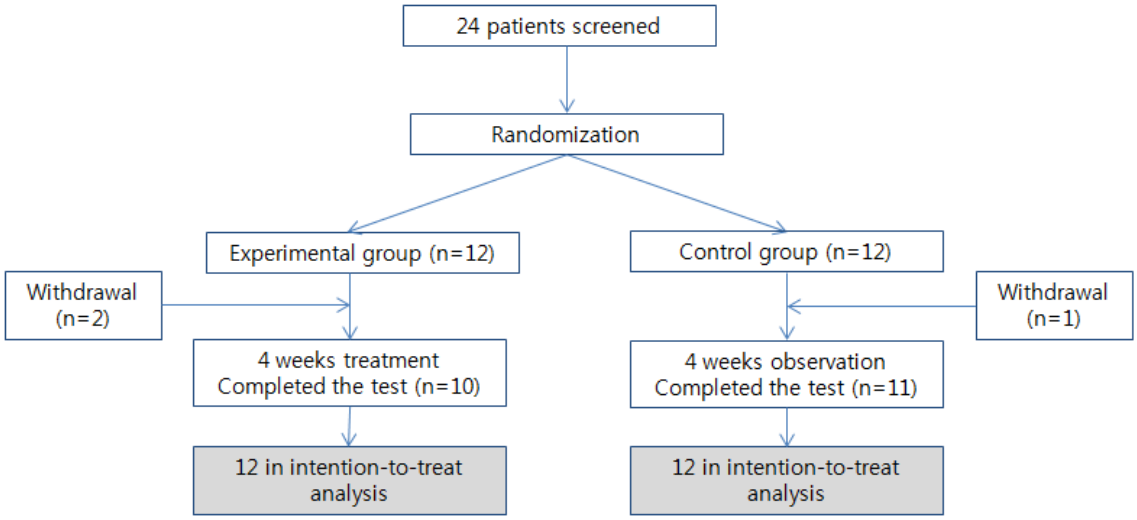

Figure 1: Study flow chart.

	Treatment group (n=12)	Control group (n=12)	P-value
Age (years)[a]	57.7 ± 10.1	61.6 ± 8.2	0.310[b]
Body weight (kg)[a]	58.3 ± 8.9	58.4 ± 8.2	0.962[b]
Height (cm)[a]	156.7 ± 4.7	154.9 ± 4.9	0.386[b]
Liver cirrhosis/chronic hepatitis, n (%)	12/0	6/6	0.014[c]
HCC, n (%)	1 (8.3)	1 (8.3)	1.000[c]
Ascites, n (%)	1 (8.3)	2 (16.7)	1.000[c]
NCC score			
Insomnia severity NCC 1-1[a]	6.8 ± 1.3	7.0 ± 1.4	0.655[b]
Insomnia inconvenience NCC 1-2[a]	6.8 ± 1.6	5.7 ± 2.1	0.139[b]
Anxiety severity NCC 2-1[a]	6.1 ± 2.6	5.1 ± 2.2	0.317[b]
Anxiety inconvenience NCC 2-2[a]	5.6 ± 2.6	4.5 ± 3.0	0.347[b]
Depression severity NCC 3-1[a]	6.6 ± 2.7	4.9 ± 2.6	0.144[b]

Depression inconvenience NCC 3-3[a]	6.0 ± 2.8	4.2 ± 3.0	0.138[b]
There was no difference in baseline characteristics between treatment and control group except for number of cirrhotic patients. [a]mean ± standard deviation ;[b]P-values are calculated by two sample t-test. [c]P-values are calculated by Chi-square test.			

Table 1: Comparison of baseline characteristics between treatment and control group.

Effects

NCC scores were evaluated at 3 time points (baseline, middle, and end of treatment; 0, 2 and 4 weeks, respectively). In treatment group, intragroup analysis revealed that the NCC scores for insomnia, anxiety, and depression all decreased significantly after 4 weeks of treatment (Figure 2).

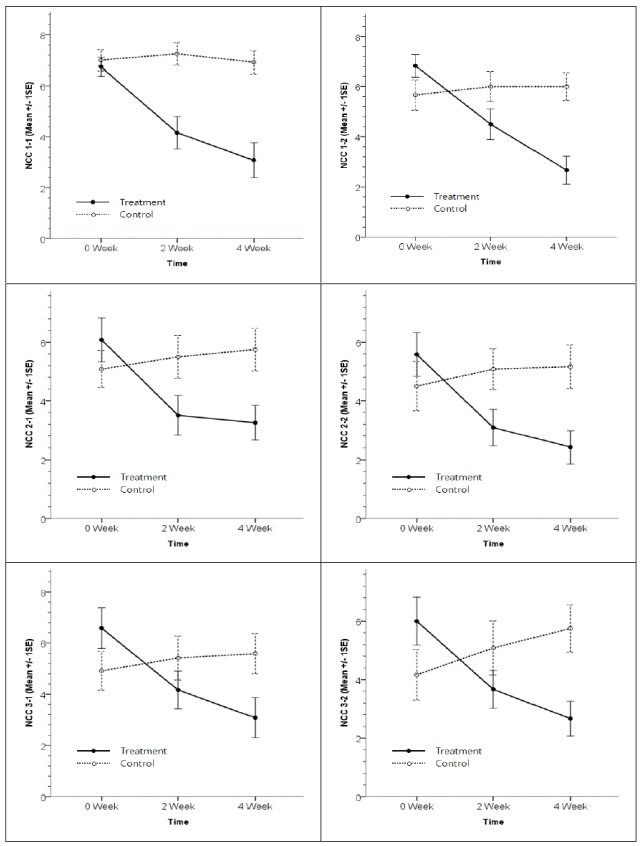

Figure 2: Change of NCC score mean value between treatment group and control group.

In treatment group, NCC scores for insomnia severity (NCC 1-1: 6.8 ± 1.3, 4.2 ± 2.2, 3.1 ± 2.4) and insomnia inconvenience (NCC 1-2: 6.8 ± 1.6, 4.5 ± 2.1, 2.7 ± 1.9) at 0, 2, and 4 weeks, respectively, decreased significantly (both, $p<0.001$). Anxiety severity scores (NCC 2-1: 6.1 ± 2.6, 3.5 ± 2.4, 3.3 ± 2.0) and anxiety inconvenience scores (NCC 2-2: 5.6 ± 2.6, 3.0 ± 2.2, 2.4 ± 1.9) at 0, 2, and 4 weeks, respectively, also decreased; these differences were significant (both, $p<0.05$). Similarly, Severity for depression (NCC 3-1) also showed a significant decrease, with 6.6 ± 2.8, 4.2 ± 2.6, 3.1 ± 2.7 ($p=0.01$). On the other hand, there were no significant changes in inconvenience of depression (NCC 3-3).

The total NCC score was calculated to evaluate the effect of acupuncture on overall psychological distress. The mean NCC score in the treatment group significantly decreased, with changes of 37.9 ± 11.9, 23.1 ± 12.4, and 17.2 ± 11.9 at 0, 2, and 4 weeks, respectively ($p<0.01$). After the last acupuncture treatment, the total NCC scores decreased 45.4%, while that of the control group tended to increase. The total NCC score of the treatment group decreased significantly compared that of the control group ($p<0.01$) (Table 2).

		Week 0	Week 2	Week 4	P-value	
Total NCC Score (Median ± SD)	Treatment	37.9 ± 11.9	23.1 ± 12.4	17.2 ± 11.9	17.070 (0.000)* 1>2>3†	20.687 (0.000)* 1>2>3†
	Control	31.3 ± 12.4	34.3 ± 13.6	35.2 ± 12.6	3.678 (0.042)* 1<2,3†	
NCC Score, National Cancer Center score *Statistically significant with p<0.05; †Multiple comparison result by contrast						

Table 2: Change of total NCC score mean value.

Safety

To evaluate the safety of acupuncture, we performed liver function tests. There were no significant differences in AST, ALT, BUN, Creatinine, T-bilirubin, Albumin, or PT (Table 3) between the treatment and control groups. Furthermore, aggravation of liver cirrhosis and primary complications (hepatic encephalopathy, hepatorenal syndrome) were not observed in either group. All patients showed good compliance. Adverse events were assessed every visit during the course of the trial, and no adverse event was observed in the course of study in any of the 21 patients.

Variables	Group	Week 0	Week 2	Week 4
AST	Treatment	47.5 ± 18.8	52.4 ± 30.4	45.4 ± 21.1
	Control	38.3 ± 16.4	36.8 ± 20.6	40.1 ± 23.0

ALT	Treatment	17.9 ± 4.3	19.7 ± 5.9	19.3 ± 7.0
	Control	30.1 ± 9.8	24.2 ± 5.1	27.8 ± 4.5
BUN	Treatment	13.0 ± 4.8	12.9 ± 3.3	12.9 ± 3.9
	Control	14.7 ± 3.9	13.4 ± 2.9	13.9 ± 3.9
Creatinine	Treatment	0.68 ± 0.1	0.67 ± 0.07	0.67 ± 0.08
	Control	0.68 ± 0.1	0.68 ± 0.12	0.7 ± 0.12
T-bilirubin	Treatment	1.32 ± 1.26	1.38 ± 1.44	1.34 ± 1.26
	Control	0.81 ± 0.46	0.81 ± 0.42	0.75 ± 0.39
Albumin	Treatment	3.95 ± 0.42	3.93 ± 0.39	3.98 ± 0.37
	Control	4.2 ± 0.32	4.05 ± 0.27	4.15 ± 0.29
PT	Treatment	14.6 ± 1.2	14.3 ± 1.2	14.3 ± 1.3
	Control	13.5 ± 0.8	12.6 ± 3.8	13.5 ± 1.0

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time.
mean ± standard deviation

Table 3: Mean change of blood composition.

Discussion

This randomized, controlled trial investigated the effect of acupuncture on psychiatric problems related with chronic liver disease. Twenty-four patients had undergone chronic liver disease including HCC, liver cirrhosis and chronic hepatitis. Two patients in treatment group and one in control group were drop-out because of private reasons without any adverse events. Twenty-one patients completed the trial. Considering significant change of NCC score of insomnia, anxiety and depression, acupuncture might give positive effect on psychiatric symptoms associated with chronic liver disease. These findings concur with our previous pilot study.

The acupuncture points used in this study were selected based on previous studies. Liver disease can lead to the stagnation of liver qi, inducing emotional imbalance. Based on this pathogenesis, we chose LI4 and LR3 named 'four gates' points those were determined to regulate flow of the liver qi. In addition, we selected PC6, SP4, HT7 for regulating the overall flow of qi in the body based on those used in several studies [19-23] and GV20, EX-HN1 were added from the extra-meridian points for calming and relaxing effects [17]. The acupuncture treatment was administered 3 times a week for 4 weeks 12 sessions. Single-sided PC6, SP4, HT7, GV20, EX-HN1 and both sided LI4, LR3 total nine acupuncture points were used.

The BDI and Hamilton depression scales have been used as indices for depression, anxiety, and insomnia in clinical trials [24,25]. We used the NCC index to evaluate anxiety, depression, and insomnia. This index was developed by psycho-oncology experts in Korea using standard diagnostic principles of psychological distress and information from literature reviews. NCC includes self-reporting questionnaires to document the severity of insomnia, depression, anxiety, or limitations of daily life. Although this tool was developed to assess distress in cancer patients, it met our assessment needs, focusing on the alleviation of symptoms rather than the eradication of liver disease. At baseline, all patients recorded NCC scores greater than 4 points, which indicates the need for the aid of mental health professionals. After 2 weeks, NCC scores in the treatment group were less than 4 points, while the control group showed no improvement in psychiatric symptoms.

Except the inconvenience of depression (NCC 3-2), each NCC scores for mental stress decreased significantly compared with those of control group. There were no evident adverse events, such as subcutaneous bleeding, following acupuncture. Four weeks of acupuncture treatment improved the symptoms of insomnia, anxiety, and depression compared with that of control group, furthermore, there was no side effect such as aggravation of liver function and complications associated with liver disease.

Several studies have shown benefits of acupuncture including improvements of emotional and physical well-being in depressive disorders [26-28]. However, patients with chronic liver disease also suffer from accompanied psychiatric disorders such as anxiety, insomnia, depression et al. Unlike other disease, use of medication to treat symptoms of anxiety, depression and insomnia in patients with chronic liver disease is restricted for fear that it should progress liver dysfunction. Therefore a treatment to improve anxiety, depression and insomnia without aggravating liver disease is in much need. Acupuncture may be a safe and effective treatment for psychiatric distress of liver disease.

One study showed more improvement of irritable bowel syndrome when permitted to have a relationship with the practitioner [25]. We attempted to minimize interaction with patients, since acupuncture treatment could foster a relationship between patients and practitioners, consequently result in a placebo effect [29-31]. Therefore, we restricted talks with patients except for advice agreed upon before treatment.

The present study had several limitations. First, the study consists of small sample size and was conducted only for female patients. Second, the design of the study is not optimal. In control group, there was only

observation without any sham treatment. Third, the measurement tool of psychiatric disorders was not widely known worldwide.

In spite of these limitations, this is the first study to show the feasibility and safety of acupuncture for the treatment of psychiatric disorders accompanied with chronic liver disease. The results of this study showed a mean reduction of 45.4% in total NCC scores in treatment group, whereas no reduction in control group. This study's result can provide preliminary data indicating that acupuncture can be a good alternative treatment for insomnia, anxiety, and depression accompanied with chronic liver disease patients.

Further retrospective clinical trials using a larger patient cohort will be needed to verify the effects and safety of acupuncture for insomnia, anxiety, and depression associated with liver disease. Also, research using sham control group may be warranted to investigate the effects of acupuncture.

Conclusion

In this study, we administered acupuncture to patients with liver cirrhosis, chronic hepatitis, and HCC, conditions that contraindicate the use of medications for anxiety, depression, and insomnia. We observed that acupuncture improved symptoms of insomnia, anxiety, and depression in patients with liver disease. Furthermore, we encountered no complications of acupuncture treatment or aggravation of liver cirrhosis, HCC, or impaired liver function.

Footnotes

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Author Disclosure Statement: No competing financial interests exist.

Ethical approval: This study was registered at the Institutional Review Board of Daegu Catholic University Hospital, Daegu, South Korea. All work was undertaken following the provisions of the Declaration of Helsinki.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing: All data can be accessed when you ask to corresponding author.

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