THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 19, Number 9, 2013, pp. 733–739

DOI: 10.1089/acm.2011.0637

Original Articles

Effects of Electroacupuncture on Depression and the Production of Glial Cell Line–Derived Neurotrophic Factor Compared with Fluoxetine: A Randomized Controlled Pilot Study

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Abstract

Background and Objective: Postmortem studies indicate that the number and density of glial cells are reduced in different brain regions of patients with depression. Glial cell line–derived neurotrophic factor (GDNF) plays an important role in the pathogenesis of depressive disorder (DD) and might be a biomarker for damage to nerve cells. In this study, we compared the therapeutic effects of electroacupuncture (EA) and fluoxetine, a serotonin reuptake inhibitor, on DD patients, focusing on the serum level of GDNF.
Design: This was a prospective, randomized clinical trial.
Setting: Seventy-five patients with DD from the Department of Acupuncture, Beijing Hospital of Traditional Chinese Medicine, were recruited.
Intervention: Twenty patients were treated with acupuncture for 6 weeks on the acupoints of Baihui (DU20) and Zusanli (ST36). Sixteen patients were treated with acupuncture for 6 weeks on the acupoints of Taichong (LR3), Sanyinjiao (SP6), Neiguan (PC6), and Shenmen (HT7), and constituted the electroacupuncture control group. The patients received acupuncture treatment five times per week. Twenty-five patients were treated with oral fluoxetine (20 mg/day) for 6 weeks.
Outcome measures: All subjects were evaluated by the Hamilton Depression Rating Scale at four time points (0 [baseline], 2, 4, and 6 weeks after treatment). Serum GDNF was quantified in duplicate by enzyme-linked immunosorbent assay (ELISA).
Results: EA and fluoxetine had similar curative effects on DD patients. EA had a faster onset of action, better response rate, and better improvement rate than fluoxetine. Both fluoxetine and EA treatment restored the normal concentration of GDNF in the serum of DD patients.
Conclusion: EA treatment for depression is as effective as a recommended dose of fluoxetine. However, EA demonstrates an advantage in the regulation of the production of GDNF compared with fluoxetine.

Introduction

Depressive disorder (DD) is a heterogeneous disorder characterized by a significant and lasting decline in mood. DD is the major cause of disability and premature death by suicide.[1] Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has been widely used for treating depression. However, fluoxetine has several side effects, such as nausea, headache, weight gain, diarrhea, dizziness, insomnia, anxiety or agitation, tremor, sexual dysfunction, and occasionally hyponatremia.[2]

As a nonpharmacologic intervention, acupuncture has a long history in the treatment of patients with psychological and spiritual symptoms in China, Japan, and Korea.

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Acupuncture is a complementary and alternative medicine that has been applied to treat psychiatric and emotional disorders in Western countries during the past few decades.[3] Acupuncture consists of inserting fine needles through the skin at several special points on the body. The acupuncture stimulation process can be enhanced by an electroacupuncture (EA) apparatus. EA can alleviate the symptoms of DD patients without detectable negative side effects.[4–6]

However, the underlying mechanisms of EA treatment for depression are unclear. Glial cell line–derived neurotrophic factor (GDNF) is a major factor in the pathogenesis of depression, and its production could reflect the degree of damage to nerve cells.[7–10] As a member of the transforming growth factor β family, GDNF is considered one of the most potent physiological factors acting on serotonergic and dopaminergic neurons.[11] GDNF and its receptors are widely distributed in various brain regions and have pronounced effects on the regulation of growth, survival, and migration of central nervous system (CNS) and peripheral neuronal cells.[12,13]

Based on reports from practitioners of Traditional Chinese Medicine (TCM) and on our long-term experience in the clinic, we hypothesized that acupuncture could improve DD symptoms. Such an effect would make acupuncture a good choice for nonpharmacological intervention due to its advantages of safety and absence of side effects.[4–6] To achieve good control in stimulating the acupoints, we used EA treatment rather than traditional hand-guided acupuncture. In the selection of points, we compared two combinations of acupoints: one based on our long-term clinical experience and another as the EA control based on the acupoints frequently used for DD-associated symptoms in China.[5] In this way, we designed a study to compare the therapeutic effects of EA and fluoxetine on DD patients by assessing Hamilton Depression Rating Scale (HDRS) scores. Moreover, to provide more objective scientific evidence, we measured GDNF in the serum of DD patients before and after treatment. This study should improve our understanding of the efficacy of acupuncture in DD treatment via clinical observation and biomarker measurement.

Materials and Methods

Subjects and setting

Subjects voluntarily responded to an announcement posted in the Beijing Hospital of Traditional Chinese Medicine. The program was supported by two grants from the Chinese government that allowed us to provide several free clinical services, including routine blood and urine tests. The recruitment period was from April 2007 to November 2008. All participants were outpatients in the Department of Acupuncture, Beijing Hospital of Traditional Chinese Medicine, which specializes in TCM treatments of depression. The patients showed interest in the study because they expected to benefit from a better treatment effect with fewer side effects. Clinicians provided a detailed explanation of the study to the prospective participants and invited them to participate in the study. A total of 118 patients with depression symptoms, ranging from 18 to 70 years old, agreed to participate and were invited for an interview. During this interview, the patients were screened for DD with the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV criteria and the 24-item HDRS. Eligible patients were asked to finish the baseline questionnaire and undergo normal blood and urine tests. After eligible patients were identified and provided informed consent, they were randomly assigned to one of three intervention groups. Figure 1 illustrates the details of recruitment, intervention, and measurement.

The inclusion criteria included the following: (1) age between 18 and 70 years; (2) fulfillment of the DSM-IV criteria (American Psychiatric Association, 1994) based on the Standard Clinical Interview for DSM-IV; and (3) a score of 20 or greater on the 24-item Hamilton Depression Rating Scale for each symptom, as evaluated by a trained physician.[14] The exclusion criteria were concomitant psychiatric illnesses, mental retardation, alcohol or drug abuse, severe somatic illnesses, positive medical history for cerebral diseases, and obesity. Patients who had a history of infection, known autoimmune disease, electroconvulsive therapy, or who used immunosuppressive agents or immunostimulants within 6 months were excluded. Pregnant or breastfeeding women were excluded. Each patient received a routine blood and urine test. The laboratory tests were repeated after 6 weeks. All patients had a normal electrocardiogram (ECG).

Following the baseline assessment, the participants were randomly assigned to the electroacupuncture treatment group, electroacupuncture control group, or fluoxetine group, according to a random number table prepared in advance. Block randomization was designed by an independent biostatistician, who was not involved in recruitment, according to a computerized list. Opaque envelopes with the information describing the group allocation were transferred to another nurse who was not involved in the study, and these were sequentially numbered. When participants provided written consent to enroll in the study, the study coordinator opened the envelope and allocated participants to treatment groups.

The study was undertaken according to the principles of the Declaration of Helsinki. The study procedure received formal approval from the Ethics Committee of the Institutional Review Board, and all patients provided written informed consent before participating in the study.

Procedures

Participants received acupuncture treatments five times per week for 6 weeks. At the same time, participants in the fluoxetine group were treated with oral fluoxetine (20 mg/day) for 6 weeks. Each patient's symptoms were evaluated by a trained physician using HDRS before treatment (0 weeks) and after 2, 4, and 6 weeks of treatment. Serum GDNF was measured before and after 6 weeks of treatment.

Acupuncture intervention

DD patients treated with EA were divided into two groups. Group 1, the treatment group, contained 20 patients who underwent EA treatment for 6 weeks on the acupoints of Baihui (DU20) and Zusanli (ST36) synchronously. The selection of acupoints was based on our long-term experience in the clinic. Group 2, the EA control group, included 16 patients who underwent EA treatment for 6 weeks on the acupoints of Taichong (LR3), Sanyinjiao (SP6), and Neiguan (PC6) and Shenmen (HT7), whose selection was based on the acupoints frequently used for DD-associated symptoms in China.[5]

The same type of sterile acupuncture needles (Huatuo Company, 0.30×40 mm) were used after conventional

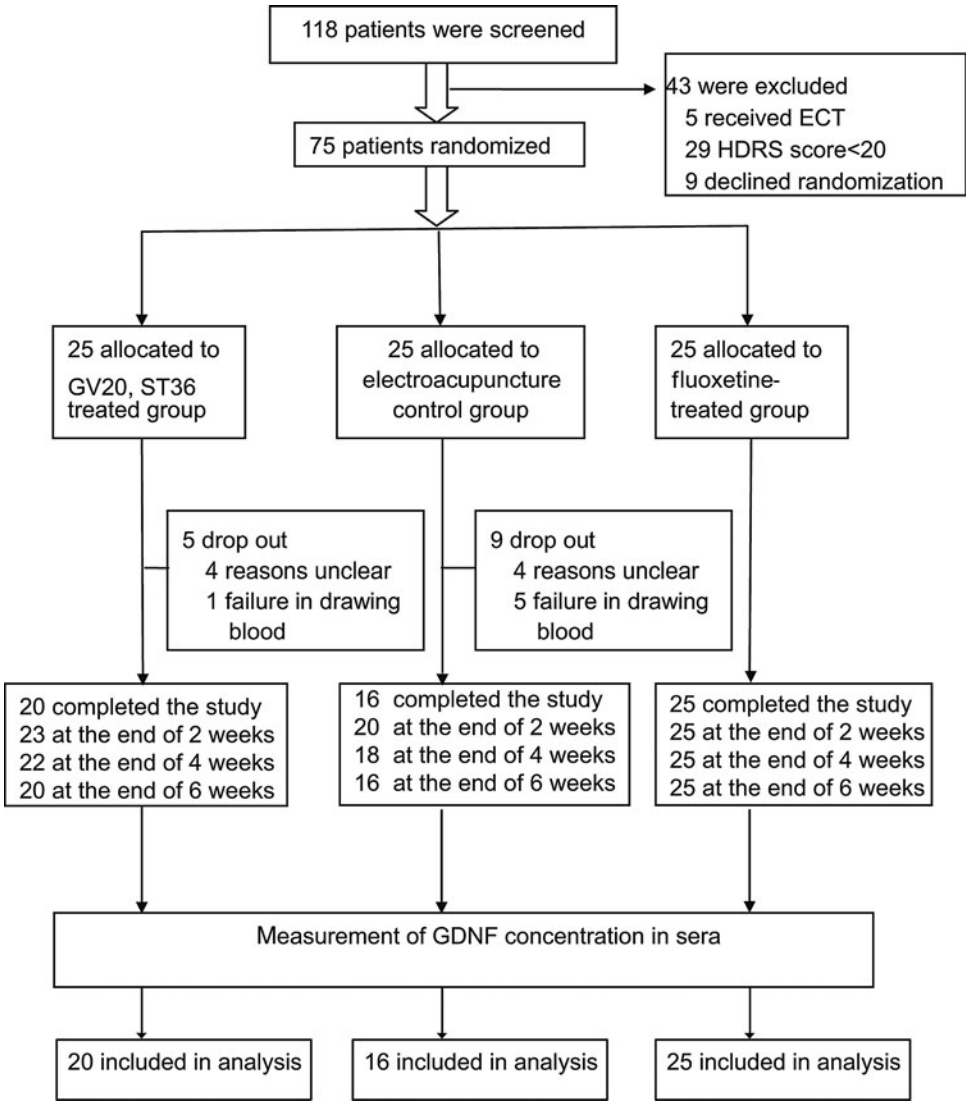

FIG. 1. Trial flow diagram.

disinfection in each EA group. The acupoints applied in this study were located according to the Chinese National Criteria for Point Location (GB12346-90). The directions of needling were based on *Meridians and Acupoints*, which is the textbook used in national TCM universities in China. The depth of the needles inserted into the skin varied between 0.25 cm and 0.40 cm, depending upon the bodily form of the patient. The reinforcing-reducing stimulation was applied until the "*DeQi*" sensation was obtained. *DeQi* means that patients experience a certain feeling from the acupuncture, which is a mixture of sourness, numbness, distension, and pain.

The needles at Baihui (DU20) and Zusanli (ST36) or at Taichong (LR3) and Sanyinjiao (SP6) were connected to an electroacupuncture apparatus (KWD-808 II Acupuncture Stimulator; Great Wall brand, Shanghai, China), with a frequency of 3 Hz and continuous waves based on the patient's tolerance. EA was applied once daily for 30 minutes at a time. The patients received EA treatment 5 times per week. Acupuncture interventions for the treatment and control groups were manipulated by the same acupuncturists, who have 5 years of training in acupuncture and TCM and more than 2 years of clinical experience. Figure 2 shows how the needles are wired up.

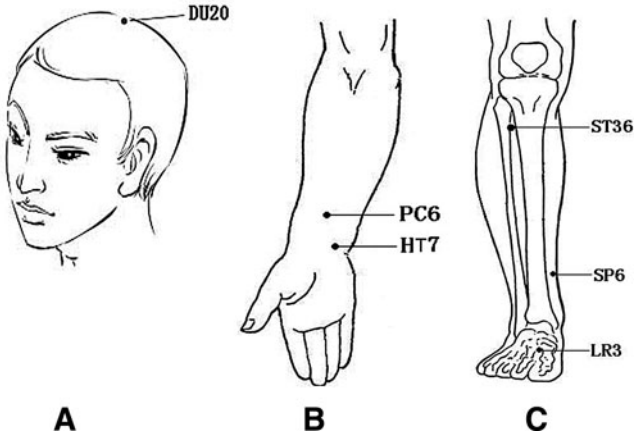

FIG. 2. Acupuncture points **(A)** DU20, **(B)** PC6 and HT7, and **(C)** ST36, SP6, and LR3.

Table 1. The Characteristics of Patients Treated with Electroacupuncture or Fluoxetine

	Patients with depression		
	EA-treated group	*EA control group*	*Fluoxetine-treated group*
Group size	20	16	25
Gender			
Male	8	3	3
Female	12	13	22
Age	43.10 ± 13.86 (23 ~ 66)	42.56 ± 10.70 (27 ~ 66)	40.72 ± 12.80 (25 ~ 70)
Weight	59.95 ± 8.79	59.44 ± 5.46	56.32 ± 6.50
Height	165.75 ± 7.12	163.50 ± 6.38	163.12 ± 4.94
BMI	21.73 ± 2.02	22.27 ± 2.21	21.19 ± 2.48
Age of onset (years)	40.88 ± 14.26	39.50 ± 11.77	38.52 ± 13.24
Duration of current illness (weeks)	11.85 ± 12.55	12.63 ± 16.08	14.68 ± 13.47
Duration of total illness (years)	2.07 ± 2.50	3.20 ± 5.08	2.35 ± 4.30

Data were expressed as mean ± SD. EA, electroacupuncture; BMI, body mass index.

Demographic and clinical data

Baseline data, including age, gender, BMI, and duration of disease, were carefully recorded.

HDRS scores

HDRS scores of each patient were evaluated at 0, 2, 4, and 6 weeks of therapy. All patients had HDRS scores of 20 or higher at enrollment. Treatment response was defined as a ≥ 50% reduction in HDRS score, and great improvement was defined as a final HDRS score ≤ 15. The nonresponders were not excluded until the end of the trial, and they received alternative treatments afterward.

GDNF concentration

Blood samples taken from the patients were collected between 8:00 and 9:00 a.m. in tubes without any additive (BD Vacutainer Systems, Franklin Lakes, NJ). The serum was obtained by centrifugation at 2000 × *g* for 20 min and stored at −80°C until used. GDNF was quantified in the same experiment and in duplicates with the use of commercially available ELISA kits (R&D systems, Minneapolis, MN). The inter- and intra-assay coefficients of variation for all assays were less than 10%. In this trial, the investigator performing the assessment of GDNF concentration was blinded to treatment assignment.

Statistics

Data are presented as the means ± SD and were analyzed with the statistical analysis software SPSS, version 12.0 (SPSS, Inc., Chicago, IL). The one-sample Kolmogorov-Smirnov test was used to characterize the distribution of data. The paired-samples t-test and the Wilcoxon signed-rank test were used to compare the differences between pre-treatment and post-treatment values according to the distribution of data. One-way ANOVA or the rank-sum test was used to compare differences between groups. Repeated-measures ANOVA was used to compare the HDRS scores in patients treated with EA vs. fluoxetine at different times. Pearson's correlation analyses was performed to evaluate the relationships between GDNF level and HDRS score. All P-values are two-tailed, and a P-value of less than 0.05 was considered to indicate statistical significance.

Results

Basic features

A total of 75 patients were recruited into the study, and 25 patients were allocated to each treatment group. As shown in Figure 1, a total of 14 patients dropped out: 5 cases from the EA treatment group and 9 cases from the EA control group. In the 5 cases of dropouts from the EA treatment group, 4 cases had no reason for refusing to participate in the study, while 1 case refused because she was scared of getting blood drawn. In the 9 cases of dropouts from the EA control group,

Table 2. Hamilton Depression Rating Scale Scores Among the Three Groups

	Patients with depression			
	EA-treated group (95% CI)	*EA control group (95% CI)*	*Fluoxetine-treated group (95% CI)*	P-*value*[a]
Baseline	23.80 ± 2.93 (22.43 ~ 25.71)	22.81 ± 3.25 (21.08 ~ 24.54)	23.32 ± 3.49 (21.88 ~ 24.76)	0.356
Week 2	18.80 ± 3.11 (17.35 ~ 20.25)	18.94 ± 3.28 (17.19 ~ 20.68)	21.76 ± 4.28 (19.99 ~ 23.53)	0.014
Week 4	14.25 ± 3.51 (12.61 ~ 15.89)	14.06 ± 3.07 (12.43 ~ 15.70)	17.44 ± 3.85 (15.85 ~ 19.03)	0.003
Week 6	9.45 ± 3.17 (7.97 ~ 10.93)	9.94 ± 2.18 (8.18 ~ 11.10)	12.12 ± 4.38 (10.31 ~ 13.93)	0.161
P-value[b]	0.000	0.000	0.000	

Data were expressed as mean ± SD.
[a]*P-values* are for between-group comparisons of the three groups.
[b]*P-values* are for within-group comparisons of the three groups.
CI, confidence interval.

Table 3. The Levels of Serum GDNF Measured in the Three Groups (pg/ml)

Group	*Before treatment (95% CI)*	*After 6 weeks (95% CI)*	P-*value*[a]
EA-treated group	20.94 ± 6.82 (17.75 ~ 24.13)	24.79 ± 3.98 (22.93 ~ 26.65)	0.028
EA control group	20.43 ± 6.24 (17.10 ~ 23.75)	23.94 ± 5.67 (20.91 ~ 26.96)	0.022
Fluoxetine-treated group	20.35 ± 7.18 (17.38 ~ 23.30)	23.38 ± 4.56 (22.79 ~ 25.18)	0.021
P-value[b]	0.528	0.499	

Data were expressed as mean ± SD.
[a]*P-values* are for within-group comparisons of the three groups before and after the treatment.
[b]*P-values* are for between-group comparisons of the three groups.
GDNF, glial cell line–derived neurotrophic factor.

4 cases had no reason for refusing to participate in the study, while the other 5 cases refused due to fear of drawing blood for testing. Ultimately, we analyzed 20 patients in the EA treatment group, 16 in the EA control group, and 25 in the fluoxetine treatment group. Table 1 lists the basic patient information. There were no significant differences at baseline among the three groups with respect to age, gender, weight, height, BMI, age of onset, duration of current illness, or duration of total illness.

Changes in HDRS scores in patients treated with EA or fluoxetine

There was no significant difference among the three groups in their baseline HDRS scores ($F = 1.052$, $p = 0.356$). The therapeutic effects of the three treatments on HDRS scores were dissimilar across time (group-by-time interaction: $F = 141.338$, $p < 0.001$). As shown in Table 2, significant effects of the three treatments on HDRS scores were observed at various time points compared with the baseline ($p < 0.001$). For patients in the EA treatment group and EA control group, the HDRS scores were significantly lower at week 2 and week 4, respectively, compared with the scores of those treated with fluoxetine. However, the differences became insignificant at the endpoint (week 6) of the trial ($p = 0.161$). The three treatments demonstrated significant differences in the percentage of responders (at least a 50% reduction in the HDRS score). Both the EA treatment group and EA control group had a response rate of 75%, while the fluoxetine group had a response rate of 60%. There was also a significant difference among the three groups in the proportion of responders ($p < 0.001$). Furthermore, in the EA treatment group and EA control group, 93 and 92% of patients showed great improvement, respectively, whereas only 84% of the fluoxetine treatment group showed great improvement after 6 weeks of treatment (Ham-D ≤15). This difference among groups was significant ($p < 0.05$).

Table 4. Correlation of GDNF Levels with HDRS Scores Before and After Intervention

GDNF	*EA-treated group*		*EA control group*		*Fluoxetine-treated group*	
	r	p	r	p	r	p
HDRS	−0.343	0.030*	−0.363	0.041*	−0.152	0.293

HDRS, Hamilton Depression Rating Scale. *$P < 0.05$.

Comparison of GDNF concentrations before and after intervention

There was no significant difference in the serum GDNF concentration among the three groups before treatment. After 6 weeks of treatment, serum GDNF significantly increased in all groups compared with baseline ($p < 0.05$) (Table 3). The different treatments seemed to have similar effects on serum GDNF, as there were no significant differences in the level of GDNF among the three groups after the assigned treatment ($p > 0.05$).

The correlations between GDNF level and HDRS score were calculated separately for the three groups. As indicated in Table 4, the GDNF level was inversely correlated with the HDRS score in both the EA treatment group ($P < 0.05$) and the EA control group ($P < 0.05$). However, there was no significant correlation between the GDNF level and HDRS score in the fluoxetine group.

Discussion

EA stimulation has been used to treat various mood disorders for several decades. This study showed that the efficacy of EA was comparable to that of fluoxetine in relieving the symptoms of depression. A recent meta-analysis demonstrated that acupuncture monotherapy was as effective as antidepressants in 20 clinical trials in terms of treatment response and alleviating symptom severity.[15] It is noteworthy that EA treatment in our trial had a faster onset of action, better response rate, and better improvement rate than treatment with fluoxetine. Therefore, this is the first study, to our knowledge, demonstrating that EA works faster than antidepressants to alleviate the symptoms of DD. The baseline clinical characteristics did not differ among the groups, so they could not explain the differences in the therapeutic effects. Moreover, EA treatment offers a better adverse event profile than chemical drugs.[16,17] Thus, EA may be an effective therapy in the management of patients with depression.

Depression is classified as a component of "Yu syndrome" in traditional Chinese medicine. Yu syndrome is a sentimental disease that results from the disorder of the Qi and the brain due to seven internal emotional injuries. Its onset is related to Qi, blood, phlegm, and blood stasis, and also involves the heart, liver, spleen, and kidneys. The selection of acupoints is based on the differentiation of symptoms. The most frequently chosen acupoints are in the meridians of the heart, liver, spleen, and Du. DU20 is a major acupoint in the Du meridian, located at the vertex of the head, which is thought to be "the house of the spirit" and is named "the smart house." DU20 has the function of opening the oracles and awakening the spirit. The Du meridian goes through the spine, ascends into the brain, and meets the liver meridian at the vertex, and then diverges from the spine and enters the kidneys. Thus, it connects the brain, liver, and kidneys. Baihui (DU20) functions to modulate the nervous, endocrine, and immune systems.[18] A clinical trial has shown that DU20 plays a valuable role in treating depression.[19]

ST36 is the conjunction point of the stomach channel of the foot-yangming and is an important tonic point. Treatment at DU20 and ST36 strengthens the spleen, supplies the Qi, soothes the nerves, and balances the yin and yang, which reflects the characteristics of TCM and can be easily applied. The acupoints of DU20 and ST36 can rescue the imbalance of the 5-HT receptor, which is one of the major molecular causes of depression.[20–21] This finding provides a reliable basis for the treatment of depression. Interestingly, we observed a good curative effect in the acupuncture control group.

PC6 is the contact point in the pericardium meridian of the hand-jueyin and belongs to eight confluence points. HT7 is the original point in the heart meridian of the hand-shaoyin. Acupuncture at PC6 and HT7 is used for palpitation, poor memory, insomnia, and other maladies. LR3 belongs to the liver meridian of the foot-jueyin, which is applied to cure convulsions and spasms. SP6 is the intersection point of the liver, spleen, and kidneys. Acupuncture at PC6, HT7, LR3, and SP6 activates mainly the heart and liver meridians and can significantly improve mental and physical symptoms of depression.[19,22–24]

Alterations in GDNF concentration are a major factor in the pathogenesis of depression.[7–10] GDNF, a member of the transforming growth factor-β superfamily, was originally identified as a potent survival factor for dopaminergic neurons.[25] Later, GDNF was found to have a trophic effect on dopaminergic neurons in various neuronal subtypes of the central and peripheral nervous systems.[26–28] GDNF exerts neuroprotective effects and functions in higher-order brain activities.[29] GDNF may be involved in the etiology of neuropsychological disorders, such as mood disorders.[30–32]

In our study, serum GDNF was increased by treatment with EA or fluoxetine. Furthermore, we found a strong correlation between the HDRS score and serum GDNF level in patients receiving EA treatment. Our study is the first to report that HDRS scores reduced by EA treatment were associated with serum GDNF changes in DD patients. Our results are consistent with a recent report from a clinical study that patients with major depression expressed significantly higher concentrations of GDNF after antidepressant treatment than before treatment.[10] SSRIs, tricyclic antidepressants (TCAs), and the neurotransmitter serotonin induce GDNF release in cultured cells.[33] Antidepressants may regulate GDNF synthesis and release by increasing monoamine levels.[34] It is less clear how EA affects the GDNF level in patients, but in MFB-transected rats, EA upregulates GDNF mRNA in the midbrain and the striatum.[35] Another study has shown that acupuncture significantly stimulates the expression of GDNF in neurons.[36] Thus, we speculate that EA can improve psychological symptoms in DD patients by affecting the expression of GDNF and stopping or slowing degeneration.

This trial was a preliminary study with some limitations. First, we did not measure side effects. Therefore, this study provides no evidence that EA treatment has fewer side effects than fluoxetine. In general, the use of acupuncture for the treatment of DD patients shows good compliance related to its high efficacy because the only major side effect of both EA and manual acupuncture is (tolerable) pain. Second, our sample size was relatively small. A future trial with more patients will be beneficial to demonstrate the therapeutic role of EA in depression. Third, menstrual cycles and the timing of the study were not taken into consideration, but menstrual status could exert substantial effects on inflammation when controlled in a larger sample. Fourth, blood samples were only collected at the beginning and end of treatment. Thus, we could not observe the changes in GDNF at different points during treatment. Finally, our study suffers from a loss of complexity, as only GDNF was measured. In future trials, additional biomarkers, including cytokines, should be tested. Future research should not only emphasize the indexes used as depression biomarkers but also focus on the connections between immune function and different neuroendocrine factors. Longitudinal studies will be necessary to identify the pathological mechanism of EA in treating depressive disorder.

Conclusions

This study demonstrated that EA has the same therapeutic effects as the conventional drug fluoxetine in the treatment of patients with DD. The action of EA may be associated with the alteration of GDNF concentration. Larger-scale studies are required to confirm our results.

Acknowledgments

This work is sponsored by a grant (2006AA02Z432) from National Program for Biomedical Hightech, the Ministry of Science and Technology, China P.R., and a grant (04-05LP10) from the National Program for Traditional Medicine, State Administration of Traditional Chinese Medicine, China P.R.

Disclosure Statement

No competing financial interests exist.

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