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Improvement in quality of life in depressed patients following verum acupuncture or electroacupuncture plus paroxetine

A randomized controlled study of 157 cases

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Abstract

Depressed patients with scores of 17 or more on the 17 items of the Hamilton Depression Rating Scale were treated with the antidepressant drug paroxetine. They also underwent verum acupuncture or electroacupuncture at *Baihui* (GV20) and *Yintang* (GV29). The World Health Organization Quality of Life Scale Brief Version showed a significant increase in the total scores of patients who underwent verum acupuncture and electroacupuncture for 6 weeks compared with those who were given paroxetine only; significantly increased physical domain and social relationship scores in verum acupuncture patients compared with paroxetine only; and significantly elevated psychological domain scores with electroacupuncture compared with paroxetine only. These results indicate that both verum acupuncture and electroacupuncture can improve quality of life in depressed patients undergoing paroxetine treatment.

Key Words

acupuncture; electroacupuncture; depression; paroxetine; World Health Organization Quality of Life Scale Brief Version; quality of life; Chinese medicine; neural regeneration

Research Highlights

(1) The World Health Organization Quality of Life Scale Brief Version was used to evaluate the quality of life of depressed patients undergoing acupuncture plus paroxetine treatment. Scores for physical function and social relationships were significantly elevated, as were those in the psychological domain in patients undergoing electroacupuncture.
(2) The four-factor domain was superior to the six-factor domain in evaluating quality of life in depressed patients treated with acupuncture plus antidepressant drugs.

Abbreviation

WHOQOL-BREF, World Health Organization Quality of Life Scale Brief Version

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INTRODUCTION

Antidepressant drugs are commonly used to treat depression, effectively reducing the risk of recurrence[1-7]. However, about 50% of depressed patients have not been diagnosed, and some patients respond poorly to antidepressant drugs. Moreover, clinical studies show significant adverse effects of antidepressant drugs, and a new generation of antidepressant drugs remains under investigation[8-11]. Previous studies have demonstrated that the traditional Chinese medicine acupuncture, which has been extensively used to treat depression[12-14], has significantly fewer adverse effects and greater safety than antidepressant drugs[15-17]. Verum acupuncture performed in 20 depressed patients ameliorated the condition to a certain degree, and 40% of patients said that they had experienced the expected effects[18]. In a meta-analysis of 833 patients in nine studies[14], the effects of verum acupuncture alone were similar to those of antidepressant drugs alone.

However, use of acupuncture alone in the treatment of depression can also be unsatisfactory[19]. In a previous study acupuncture was used to treat 30 depressed patients who had responded poorly to antidepressant drugs; this treatment was safe and effective[20]. In addition, verum acupuncture or electroacupuncture in combination with fluoxetine had superior effects in treating depression compared with fluoxetine alone[21-23]. Thus, a combination of acupuncture and antidepressant drugs may be an option for the treatment of depression. However, there is no evidence to confirm its efficacy and reliability due to a limited number of relevant studies[14]. Chinese studies have shown paroxetine to have superior efficacy and safety over other antidepressant drugs[24-25]. Therefore, the present study combined acupuncture at *Baihui* (GV20) and *Yintang* (GV29)[26] with paroxetine to treat depressed patients, and evaluated the improvement in quality of life using the World Health Organization Quality of Life Scale Brief Version (WHOQOL-BREF) published in 1998[27-28].

RESULTS

Quantitative analysis of participants

One hundred and fifty-seven depressed patients were enrolled and randomly assigned to three treatment groups: drug control (paroxetine, n = 48), verum acupuncture (verum acupuncture + paroxetine, n = 53) and electroacupuncture (electroacupuncture + paroxetine, n = 56). The acupuncture points were *Baihui* and *Yintang*. Thirty patients withdrew from the study, leaving 127 cases (38 drug control, 45 verum acupuncture and 44 electroacupuncture) in the final analysis.

Baseline data analysis of participants

The number of female patients was greater than that of males. The patients were aged 20–40 years and the duration of their illness was less than 55 months. Before treatment, there were no statistically significant differences between groups in terms of gender, age and duration of illness (P > 0.05; Table 1).

Table 1 Patients' baseline data

Item	Drug control group (n = 38)	Verum acupuncture group (n = 45)	Electro-acupuncture group (n = 44)	P
Age (year)	36.0±11.2	32.5±9.6	32.9±9.3	0.243
Gender [(M/F (n)]	16/22	17/28	19/25	0.862
Duration of illness (month)	19.7±24.2	23.2±28.3	21.2±29.9	0.843

Measurement data were expressed as the mean ± SD. Comparison of age and duration of illness was conducted using one-way analysis of variance; differences in gender were compared using the chi-square test. M: Male; F: female.

Improvement of quality of life

On the WHOQOL-BREF (Table 2), compared with before treatment, only the scores for social relationships were elevated in the drug control group, but the scores for every quality of life item were significantly increased in the verum acupuncture and electroacupuncture groups after 6 weeks of treatment (P < 0.05). The total scores for quality of life were significantly increased in all three groups (P < 0.05).

Compared with the drug control group after 6 weeks of treatment, psychological domain scores and scores for spirituality were significantly increased in the electroacupuncture group (P < 0.05), and scores for level of independence and social relationships were significantly increased in the verum acupuncture group (P < 0.05). The total scores for quality of life were significantly elevated in patients who underwent verum acupuncture or electroacupuncture compared with those who received paroxetine only (P < 0.05).

On the four-domain WHOQOL-BREF, physical domain scores were significantly higher in the verum acupuncture group compared with the drug control group after 6 weeks of treatment (P < 0.05). Psychological domain scores were significantly higher in the electroacupuncture group compared with the drug

control group ($P < 0.05$; Table 3).

Table 2 Scores on the six-domain World Health Organization Quality of Life Scale Brief Version administered before and after treatment

Domain	Drug control group (n = 38)	Verum acupuncture group (n = 45)	Electro-acupuncture group (n = 44)	F	P
Physical					
Baseline	2.2±0.8	1.8±0.7	1.8±0.8	3.675	0.028
6 weeks	2.5±0.7	2.8±0.8	2.8±0.8	2.809	0.072
F	3.484	36.855	35.073		
P	0.070	0.000	0.000		
Psychological					
Baseline	2.4±0.9	2.3±0.9	2.1±0.9	1.060	0.350
6 weeks	2.7±0.7	3.0±0.6	3.1±0.7[a]	4.508	0.013
F	3.669	16.296	51.815		
P	0.063	0.000	0.000		
Level of independence					
Baseline	12.2±1.9	12.3±2.1	11.7±2.4	0.719	0.489
6 weeks	12.4±1.6	13.6±2.3[a]	13.1±2.0	3.611	0.030
F	0.545	12.761	18.995		
P	0.465	0.001	0.000		
Social relationships					
Baseline	11.9±2.6	12.2±2.9	11.1±2.5	2.055	0.132
6 weeks	13.2±2.0	14.0±2.1[b]	12.8±1.9	4.313	0.015
F	10.574	16.041	15.079		
P	0.002	0.000	0.000		
Environment					
Baseline	11.2±1.7	10.8±1.9	10.7±1.9	0.599	0.551
6 weeks	11.7±1.4	11.4±1.1	11.6±1.4	0.572	0.566
F	3.787	5.125	5.672		
P	0.059	0.029	0.022		
Spirituality					
Baseline	11.0±1.3	10.8±2.1	10.5±2.2	0.685	0.506
6 weeks	10.7±1.4	11.1±1.6	11.7±1.5[a]	4.983	0.008
F	1.554	1.294	14.863		
P	0.220	0.261	0.000		
Total					
Baseline	50.8±5.9	50.2±7.6	47.9±7.0	1.975	0.143
6 weeks	53.1±5.7	55.8±6.5	55.1±5.9	2.147	0.121
F	7.243	22.740	40.039		
P	0.011	0.000	0.000		
Increase in score	2.4±5.4	5.6±7.9[a]	7.2±7.5[a]	4.783	0.010

[a]$P < 0.05$, *vs*. drug control group; [b]$P < 0.05$, *vs*. electroacupuncture group. Higher scores represent better quality of life. Measurement data are expressed as mean ± SD.

Intergroup comparison was conducted using one-way analysis of variance; intragroup differences were compared using analysis of variance of repetitive measurements. Intergroup comparison of data with significant differences compared with baseline was conducted using covariance analysis.

DISCUSSION

In treatment of depression with Mianserin and acupuncture, the effects of acupuncture were not predominant and may have been only a placebo effect[29]. The results of the present study show that the effects of electroacupuncture + paroxetine were better than verum acupuncture + paroxetine, indicating differences in effect among different acupuncture methods. Experience and manipulation during needling may play a major role[30-31]. Our results also show that electroacupuncture + paroxetine was superior in improving patients' psychological domain compared with verum acupuncture + paroxetine, and verum acupuncture + paroxetine had the greatest effect on improving the physical domain and social relationships. Wang *et al* [32] suggested that acupuncture may produce cheerful feelings in patients through the endopioid peptide system and thereby attenuate anxiety[32]. In the present study, the effects of electroacupuncture and verum acupuncture in combination with the antidepressant drug paroxetine differed, possibly due to the greater intensity of stimulation produced by electroacupuncture, which was more effective in eliminating negative emotions than verum acupuncture, However, excessive stimulation may cause discomfort. Verum acupuncture is relatively gentle, and can better control pain.

Table 3 Scores on the four-domain in World Health Organization Quality of Life Scale Brief Version administered before and after treatment

Domain	Drug control group (n = 38)	Verum acupuncture group (n = 45)	Electro-acupuncture group (n = 44)	F	P
Physical					
Baseline	14.4±2.2	14.1±2.3	13.6±2.5	1.217	0.300
6 weeks	14.9±2.1	16.3±2.8[a]	15.9±2.4	3.586	0.031
F	2.176	28.754	42.393		
P	0.149	0.000	0.000		
Psychological					
Baseline	13.3±1.7	13.0±2.5	12.6±2.8	1.031	0.360
6 weeks	13.3±1.9	14.1±2.0	14.8±2.0[a]	5.903	0.004
F	0.006	7.202	36.639		
P	0.940	0.010	0.000		
Social relationships					
Baseline	11.9±2.6	12.2±2.9	11.1±2.5	2.055	0.132
6 weeks	13.2±2.1	14.0±2.1[b]	12.8±1.9	4.313	0.015[c]
F	10.574	16.041	15.079		
P	0.002	0.000	0.000		
Environment					
Baseline	11.2±1.7	10.8±1.9	10.7±1.9	0.599	0.551
6 weeks	11.7±1.4	11.4±1.1	11.6±1.4	0.572	0.566
F	3.787	5.125	5.672		
P	0.059	0.029	0.022		

[a]$P < 0.05$, *vs*. drug control group; [b]$P < 0.05$, *vs*. electroacupuncture group. Higher scores represent better quality of life. Measurement data are expressed as mean ± SD.

Intergroup comparison was conducted using one-way analysis of variance; intragroup differences were compared using analysis of variance of repeated measurements. Intergroup comparison of data with significant differences compared with baseline was conducted using covariance analysis.

The sample size in the present study was small, so we did not include sham needling + paroxetine or needling + placebo groups. Thus, we cannot exclude the possibility of an effect of acupuncture on paroxetine treatment. Moreover, we did not assess the patients' quality of life regularly, so information during treatment was not obtained. However, we confirmed efficacy of acupuncture in combination with paroxetine in treating depression. In addition, four-domain evaluation eliminated the influence of an unstable baseline and was superior to the six-domain WHOQOL-BREF.

In conclusion, adjuvant treatment with acupuncture can significantly improve quality of life in patients receiving paroxetine, and electroacupuncture was superior to verum acupuncture. Verum acupuncture + paroxetine was predominantly effective on physical function and social relationships, whereas electroacupuncture + paroxetine mainly improved psychological status.

SUBJECTS AND METHODS

Design

Prospective randomized, controlled study.

Time and setting

The study was performed in Nanfang Hospital, First Hospital of Southern Medical University, Guangzhou Overseas Chinese Hospital, First Hospital of Jinan University, and Guangdong 999 Brain Hospital, China from December, 2008 to October, 2010.

Subjects

Depressed patients admitted to Nanfang Hospital, First Hospital of Southern Medical University, Guangzhou Overseas Chinese Hospital, First Hospital of Jinan University and Guangdong 999 Brain Hospital were enrolled.

Diagnostic standards

Depression was diagnosed according to the International Classification of Disease and Diagnostic Standards for depression[33]. The depression had persisted for ≥ 2 weeks and the patients had no history of hypomania or mania.

Inclusion criteria

Patients with scores of 17 or more on the 17 items of the Hamilton Depression Rating Scale[34], of either gender and aged between 18 and 60 years, were selected.

Exclusion criteria

Patients with bipolar depression, who had participated in other clinical trials in 4 weeks before the present study, or who were taking or coming off antidepressant drugs. Neither pregnant nor lactating women were included. People suffering severe diseases of the brain or other systems, and those who had planned or attempted suicide were also excluded.

Participation criteria

Treatment was terminated in subjects with poor compliance, who did not undergo acupuncture according to regulations, who experienced physiopathological changes, who was intolerant of or hypersensitive to paroxetine, who developed adverse effects or who may have become pregnant during the treatment.

Informed consent was obtained from all participants. The study was approved by the *Administrative Regulations on Medical Institution*, issued by the State Council of China[35].

Methods

Random grouping

Randomization method: centralized randomization and random number allocation were conducted by the Center for Evidence-Based Medicine, Beijing University of Chinese Medicine. Once the 157 subjects had signed their informed consent, the researchers called the center to obtain random numbers, which were generated using SAS 6.12 statistical software (Raleigh, NC, USA).

Randomization concealment: patients were grouped during centralized randomization by the Center for Evidence-Based Medicine, Beijing University of Chinese Medicine and coded as A, B or C. Random codes were also assigned according to research center number and subject number, and the patients received the corresponding intervention according to the research workbook and random codes.

Single blind setting: blinding was not used in patients, but in outcome evaluation and data input and for the statistics researcher. All data were checked and logged in. The principal researchers and statisticians discussed the statistical plan, followed by unblinding and signing of the allocation concealment.

Intervention

Patients in the drug control group were treated with paroxetine (Glaxo Smith Kline, London, UK; No. H10950043). The verum acupuncture and electroacupuncture groups were treated with paroxetine combined with acupuncture. The drug dose was 10 mg/d for the first 2 days, then 20 mg/d until the end of the treatment, administrated orally once per day after breakfast for 6 consecutive weeks.

Electroacupuncture group:
Acupoints: *Baihui* and *Yintang* were the principal points; *Fengfu* (GV16), bilateral *Fengchi* (GB20), *Dazhui* (GV14), bilateral *Neiguan* (PC6) and bilateral *Sanyinjiao* (SP6) were the acupoints of coordination, selected according to current data on acupoints for the treatment of clinical depression[36]. The location of the acupoints was confirmed in accordance with *the Name and Location of Acupoints: Chinese National Standards*[37]. *Baihui* was located at the intersection of the highest point of the ear lobe and the medial line of the head; *Yintang* was located between the frontal region and the two eyebrows; *Fengfu* was located 1 cun vertically superior to the medial posterior hair margin; Fengchi was inferior to the nuchal occipital bone; *Dazhui* was at the hollow of the posterior medial vertebral spine at the seventh cervical vertebra; *Neiguan* was at the medial forearm, 2 cun superior to the wrist crease; and *Sanyinjiao* was located 3 cun superior to the medial malleolus of the medial leg.
Needles: Hwato stainless steel acupuncture needles (Suzhou, Jiangsu, China), (25–40) × (0.25–0.30) mm.
Acupuncture methods: the patient was placed in a sitting position for acupuncture at *Fengfu* and *Dazhui*. The needle was not left in place at the acupoints. The patient was then placed in the dorsal position for acupuncture at *Baihui*, *Yintang* and other acupoints.
During needling of *Fengfu*, the patient was asked to sit with his or her arms on the table, head sloping slightly anterior and nuchal muscle relaxed. The needle was inserted slowly in the submaxillary direction to a depth of 2.0–3.0 cm. After *Deqi*, the needle was slowly and gently twisted through 90°–180°, 60–90 times/minute for 30 seconds. It was then withdrawn slowly and pressure was applied to needle hole.
During needling of *Dazhui*, the patient was sitting or prone with the head bowed to expose the spinous process of the seventh cervical vertebrae. The needle was inserted vertically from the inferior spinous process to a depth of 3.0–3.5 cm. After *Deqi*, the needle was slowly and gently twisted through 90°–180°, 60–90 times/minute for 30 seconds. It was then withdrawn slowly and pressure was applied to the needle hole.
During needling of *Baihui*, the patient was placed in the dorsal position. The needle was inserted slowly backward to a depth of 1.5–2.5 cm. It was not lifted or thrusted, but only twisted gently until *Deqi*.
During needling of *Yintang*, the patient was placed in the dorsal position. The needle was inserted slowly upward to a depth of 1.5–2.5 cm. It was not lifted or thrusted, but only twisted gently until *Deqi*.
During needling of *Fengchi*, the patient was placed in the dorsal position. The needle was inserted from the left and right *Fengchi* acupoints to a depth of 2.0–2.5 cm, then twisted gently until *Deqi*.
During needling of *Neiguan*, the needle was inserted vertically to a depth of 1.5–2.5 cm, then twisted gently until *Deqi*.
During needling of *Sanyinjiao*, the needle was inserted vertically to a depth of 2.0–2.5 cm, then twisted gently until *Deqi*.
Baihui, *Yintang* and bilateral *Fengchi* were stimulated using Han's acupoint nerve stimulator (LH-202H; Beijing, China). The positive electrode of one set of electric wires was connected to *Baihui* and the negative electrode was connected to *Yintang*; the other set of wires was connected to bilateral *Fengchi*, with the positive and negative electrodes alternated between the left and right sides at each treatment. A disperse-dense wave, 2/15 Hz, was used, and the current was controlled within tolerance (skin micromovement). Each electroacupuncture lasted for 30 minutes.
The needle was left in place for 30 minutes at the other acupoints, with needling once after 15 minutes for 5–10 seconds.
Duration of treatment: Acupuncture was conducted every 2 days, three times per week, for 6 weeks in addition to drug treatment.
Verum acupuncture group: The principal points, acupoints of coordination, needles, acupuncture methods and duration of treatment were the same as for electroacupuncture. Needles at all acupoints were left in place for 30 minutes.

WHOQOL-BREF evaluation of quality of life

The WHOQOL-BREF originally covered six domains: physical function, psychological domain, level of independence, social relationships, environment and spirituality. Following modifications, level of independence and spirituality were included in the physical function and psychological domains[27, 38-39] to produce a four-domain evaluation. Patients were assessed at the beginning of treatment and 6 weeks after treatment to investigate changes in their quality of life.

Statistical analysis

Measurement data were expressed as the mean ± SD and analyzed using SPSS 13.0 software (SPSS, Chicago, IL, USA). The data set used for evaluation of efficacy and safety was the per protocol set. Subjects who withdrew from the study were excluded. Intergroup differences in scale evaluation scores, age and duration of illness were compared using one-way analysis of

variance; repeated measurements data were analyzed using analysis of variance of repeated measurements. Intergroup comparison of data with significant differences compared with baseline was conducted using covariance analysis. Gender data were analyzed using the chi-square test. All statistical analyses were conducted using two-sided tests, with an alpha level of 0.05.

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Author contributions: Yong Huang was the mentor and designer for this trial. Shenchang Guo recruited patients. Junqi Chen, Ganlong Li and Canghuan Zhao conducted the experiment and the result was evaluated by Shenchang Guo and Congqi Wang. Renyong Lin recorded the data. Shenghui Ma and Shanshan Qu analyzed the data. Shenghui Ma wrote the first draft of the manuscript and it was validated by Yong Huang and Zhangjin Zhang.

Conflicts of interest: None declared.

Ethical approval: This study received permission from the Ethics Committee of Guangzhou Orerseas Chinese Hospital, First Hospital of Jinan University, China. The study is registered at the Chinese Clinical Trial Register (No. ChiCTR-TRC-00000278).

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