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Use of electroacupuncture to accelerate the antidepressant action of selective serotonin reuptake inhibitors: a single-blind, randomised, controlled study

Key Messages

1. Patients treated with dense cranial electroacupuncture stimulation (DCEAS) had a significantly greater reduction in the 17-item Hamilton Rating Scale for Depression scores and clinically significant response to treatment than those having sham acupuncture (19.4% vs. 8.8%).
2. Neither sham acupuncture nor DCEAS had effects on the platelet serotonin system.
3. In the early phase of selective serotonin reuptake inhibitor treatment for depressed patients, DCEAS could be used as an additional therapy.
4. Neurobiological mechanisms responsible for DCEAS effects warrant further investigation using neuroimaging.

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Introduction

Selective serotonin reuptake inhibitors (SSRIs) are the mainstay of treatment for depressive disorders, but their outcomes are unsatisfactory.[1] A large proportion of depressed patients cannot obtain a full remission and experience relapse and functional impairment. Moreover, the delay in the onset of the action of SSRIs prolongs patients' suffering and exposes them to the risk of suicide. These shortcomings have led to the search for alternative strategies to enhance the antidepressant efficacy of SSRIs, particularly in the early phase of treatment.[2]

Acupuncture is efficacious for various types of depressive disorders, particularly in alleviating associated pain, autonomic dysfunction, sleepless, and low moods. This is thought to be associated with the fast, direct modulation of multiple central neurochemical systems. Adrenergic and serotonergic (5-HT) mechanisms in the brainstem, as well as neuronal and hypothalamic neuroendocrine systems play a pivotal role in the pathophysiology of major depression. We therefore hypothesised that electroacupuncture may enhance the antidepressant activity of SSRIs in the early phase of treatment.

Dense cranial electroacupuncture stimulation (DCEAS) involves electrical stimulation of dense acupoints on the forehead mainly innervated by the trigeminal nerve. Such acupoints modulates multiple central transmitter systems via the trigeminal sensory-brainstem adrenergic and 5-HT neuronal pathways.[3] Pilot studies have shown that DCEAS is effective in improving refractory obsessive-compulsive disorder, major depressive disorder (MDD), post-stroke depression, and MDD-associated residual insomnia.

Human platelets are terminally differentiated 5-HT-synthesising cells and are similar to 5-HT neurons in terms of synthesis, release, and receptors. Platelets have been widely used as a peripheral model for investigation of psychiatric disorders associated with the central 5-HT system. We hypothesised that DCEAS as additional treatment could produce greater clinical improvement in the early phase of SSRI treatment in patients with MDD, and that the antidepressant effects of DCEAS may be associated with changes in the platelet 5-HT system.

Methods

This single-blind, randomised, controlled trial was conducted in the Department of Psychiatry at the Kowloon Hospital of Hong Kong between May 2009 and March 2011. The study protocol was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. Based on our recent meta-analysis, a sample size of 35 patients per group could provide approximately 80% power to detect an estimated difference in the 17-item Hamilton Rating Scale for Depression (HAMD-17) score of 3 points, with an α set at 0.05 and an estimated standard deviation of 4.5 at the endpoint of 3-week treatment.

Fluoxetine (FLX) is one of the most prescribed SSRIs for major depression worldwide.[4] Unmedicated patients in both groups received orally administered FLX for 3 weeks. The dosage was initiated at 10 mg/day and escalated to an optimal dose within 1 week, based on patient response; the maximum dose was 40 mg/day. Information about the equivalent efficacy of FLX was provided to the patients.

Of 188 outpatients referred by psychiatrists, 73 were eligible and randomly assigned to receive sham acupuncture (n=35) and DCEAS (n=38). Informed consent was obtained from each patient. Each patient received nine sessions of intervention (three sessions per week) during FLX treatment. For DCEAS, acupuncture needles were inserted into six pairs of forehead acupoints and affixed with adhesive tapes to ensure allocation concealment. Electrical stimulation at a comfortable level was then delivered for 30 minutes. The acupoints were Baihui (Du-20) and Yintang (EX-HN3), left Sishencong (EX-HN1) and Toulinqi (GB15), right Sishencong (EX-HN1) and Toulinqi (GB15), bilateral Shuaigu (GB8), bilateral Taiyang (EX-HN5), and bilateral Touwei (ST8) [Fig 1]. For sham acupuncture, Streitberger non-invasive acupuncture needles were applied and affixed in the same way.[5] The forehead acupoints were outside the visual field of the subjects to ensure blinding. Patients were not told about the potential response of both procedures. To ensure consistency in acupuncture procedure, the principal investigator provided a training workshop about the acupuncture protocol. Acupuncture was performed by two registered acupuncturists who had practised Chinese medicine for over 3 years.

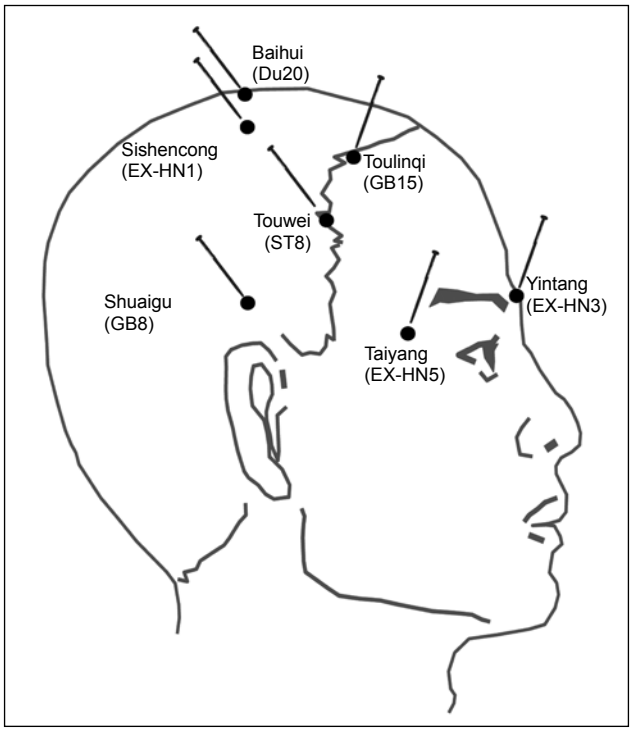

Fig 1. Acupoints used in dense cranial electroacupuncture stimulation

Outcome was assessed using the HAMD-17, the Clinical Global Impression-Severity (CGI-S), and the Chinese-version Self-rating Depression Scale (SDS) at baseline and at days 3, 7, 14, and 21. Secondary outcome measures included the treatment response and remission. Safety and tolerability were assessed using the Treatment Emergent Symptom Scale, in which adverse events were recorded at each visit. All assessments were completed by the same rater. A training workshop was provided to the rater. Both the patients and the rater were blind to the treatment allocation.

Two 10-ml blood samples were collected at baseline and day 14. Blood samples were also collected from age- and gender-matched healthy controls. Platelets and platelet-poor plasma were separated and the number of platelets was counted. The contents of platelet serotonin type 2A receptors and serotonin transporter were measured using Western blot. The concentrations of 5-HT and its metabolite 5-hydroxyindoleacetic acid were measured using reverse-phase high-performance liquid chromatography coupled with a fluorescence detector.

Results

Of the 73 patients, 63 (86%) completed the 3-week assessment. One patient in the sham group who had a history of cocaine use and two patients in the DCEAS group who did not have post-baseline assessment were excluded from analysis (Fig. 2). The proportion of females assigned to the sham group was significantly greater (97.1% vs. 69.4%, P=0.006, Chi-square test). Other baseline variables were similar in both groups (Table 1). Compliance with treatment was nearly 95%.

Changes from baseline in terms of scores of HAMD-17, CGI-S, and SDS over time revealed linear correlations (Table 2). Between-group comparisons revealed that DCEAS-treated patients had a significantly greater reduction in HAMD-17 scores at day 3 through day 21 ($P \leq 0.025$) and in SDS scores at day 3 (P=0.037) and day 21 (P=0.004). The response and remission rates were similar in both groups.

Adverse events occurred in at least 5% of the patients in both groups (Table 3). Two patients in the DCEAS group discontinued due to intolerance of acupuncture stimulation. The credibility rating in the two groups did not differ significantly.

The two groups did not differ significantly at baseline and day 14 for all platelet 5-HT parameters (Table 4).

Discussion

The use of DCEAS was effective in augmenting the

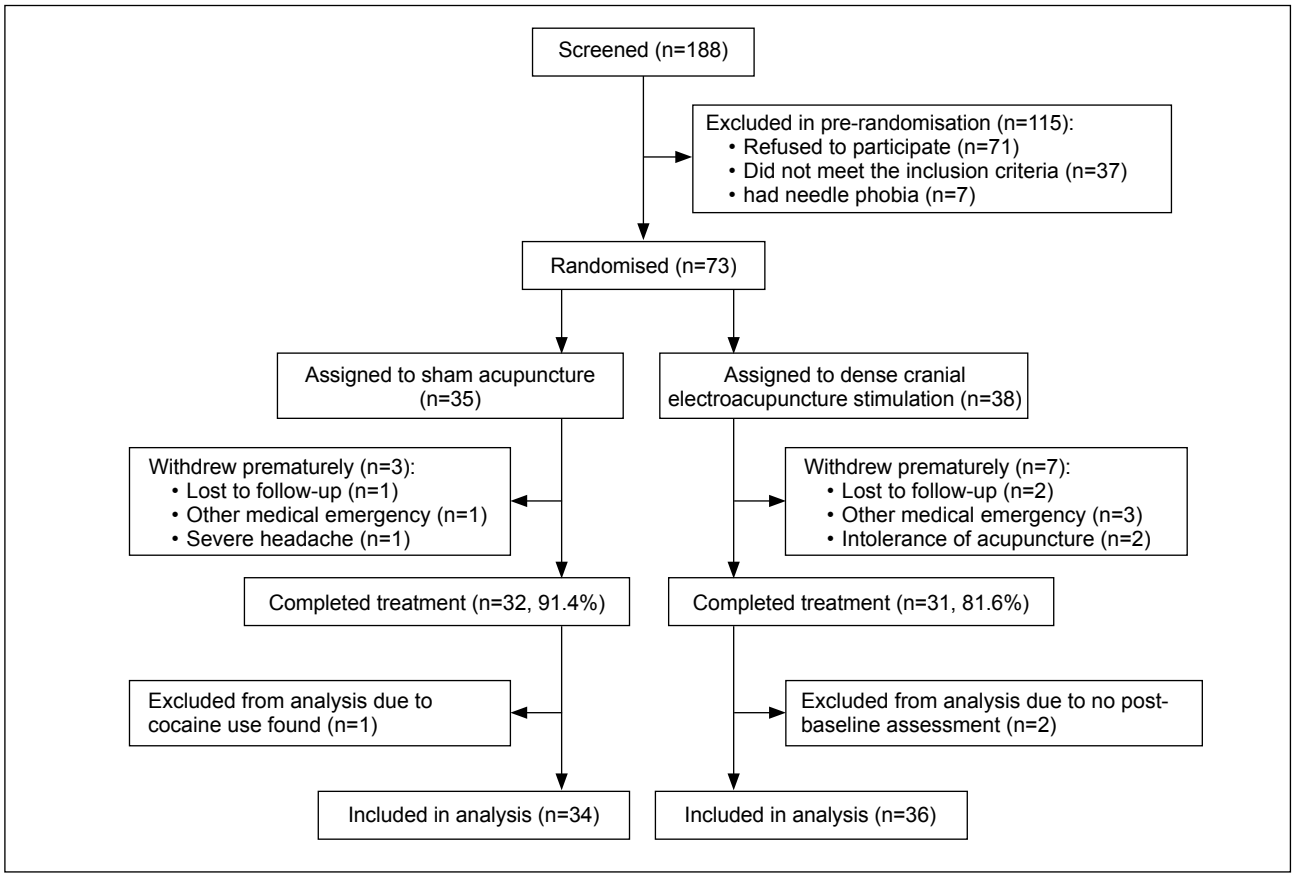

Fig 2. Flowchart of screening and patient recruitment

Table 1. Baseline characteristics of patients*

Variable	Sham acupuncture (n=34)	Dense cranial electroacupuncture stimulation (n=36)	P value (*t* or χ^2 test)
Female	33 (97.1)	25 (69.4)	0.006
Age (years)	48.2±9.8	46.3±9.9	0.414
Duration of major depressive disorder (years)	7.3±7.1	7.9±8.0	0.744
No. of previous depressive episodes	3.6±4.4	4.9±6.1	0.332
Patients with first-onset major depressive disorder	3 (8.8)	2 (5.5)	0.669
Patients with previous psychiatric admission	8 (23.5)	7 (19.4)	0.901
Patients with family members having mental illnesses	9 (26.5)	13 (36.1)	0.800
Patients with previous acupuncture treatment	22 (64.7)	24 (66.7)	0.937
Patients receiving psychotropic medications at study entry (not exceeding 1 week)	6 (17.6)	7 (19.4)	0.909
Selective serotonin re-uptake inhibitors	3	3	
Serotonin-norepinephrine reuptake inhibitors	1	1	
Mood stabilisers	1	1	
Benzodiazepines	2	2	
Baseline 17-item Hamilton Rating Scale for Depression score	23.1±3.6	23.9±3.8	0.321
Baseline Clinical Global Impression-Severity	4.3±0.5	4.4±0.5	0.760
Baseline Self-rating Depression Scale score	40.6±14.5	41.9±14.0	0.704

* Data are presented as no. (%) or mean±SD

antidepressant efficacy of FLX in patients with moderate to severe MDD, as indicated by the significantly greater reduction of HAMD-17 and SDS scores. The effect was observed as early as day 3 (after the first session of treatment). The frequency of adverse events in both groups was comparable, and only two DCEAS-treated patients discontinued treatment, indicating that it was well tolerated and safe.

The possibility of a placebo effect of DCEAS was also explored. There was no significant difference in the credibility of sham acupuncture and DCEAS, suggesting that non-inserted needling stimulation was valid and acceptable, so it was unlikely that the antidepressant

Table 2. Changes in depression scores from baseline

Variables	Mean (95% CI) change in score from baseline			P value (linear mixed effects model)
	Sham acupuncture (n=34)	Dense cranial electroacupuncture stimulation (n=36)	Between-group difference	
17-item Hamilton Rating Scale for Depression				
Day 3	-3.71 (-4.34 to -3.06)	-5.97 (-6.71 to -5.23)	2.27 (1.29 to 3.25)	0.000
Day 7	-5.82 (-6.46 to -5.18)	-6.97 (-7.71 to -6.23)	1.15 (0.17 to 2.13)	0.025
Day 14	-6.41 (-7.05 to -5.77)	-8.44 (-9.18 to -7.70)	2.03 (1.05 to 3.01)	0.000
Day 21	-6.27 (-6.90 to -5.62)	-8.66 (-9.39 to -7.91)	2.39 (1.41 to 3.37)	0.000
Clinical Global Impression-Severity				
Day 3	-0.32 (-0.42 to -0.22)	-0.44 (-0.54 to -0.34)	0.12 (-0.03 to 0.27)	0.116
Day 7	-0.65 (-0.75 to -0.55)	-0.53 (-0.63 to -0.43)	0.12 (-0.03 to 0.27)	0.116
Day 14	-0.71 (-0.81 to -0.61)	-0.71 (-0.81 to -0.61)	0.00 (-0.15 to 0.15)	1.000
Day 21	-0.74 (-0.84 to -0.64)	-0.74 (-0.84 to -0.64)	0.00 (-0.15 to 0.15)	1.000
Self-rating Depression Scale				
Day 3	-6.44 (-8.48 to -4.40)	-9.76 (-12.03 to -7.49)	3.32 (0.26 to 6.38)	0.037
Day 7	-8.82 (-10.86 to -6.78)	-9.12 (-11.39 to -6.85)	0.30 (-2.76 to 3.36)	0.851
Day 14	-11.74 (-13.78 to -9.70)	-12.38 (-14.65 to -10.11)	0.64 (-2.42 to 3.70)	0.679
Day 21	-8.38 (-10.42 to -6.34)	-13.06 (-15.33 to -10.79)	4.68 (1.62 to 7.74)	0.004

Table 3. Adverse events during treatment

Adverse event	No. (%) of patients		χ^2	P value
	Sham acupuncture (n=34)	Dense cranial electroacupuncture stimulation (n=36)		
Dizziness	15 (44.1)	11 (30.6)	0.858	0.354
Tiredness	10 (29.4)	15 (41.7)	0.672	0.412
Nausea	10 (29.4)	10 (27.8)	0.013	0.910
Excessive sweating	9 (26.5)	6 (16.7)	1.403	0.236
Headache	8 (23.5)	10 (27.8)	0.018	0.894
Transient tachycardia	8 (23.5)	9 (25.0)	0.018	0.892
Insomnia	7 (20.6)	9 (25.0)	0.024	0.877
Discomfort during needling sensation	7 (20.6)	14 (38.9)	1.985	0.159
Vomiting	4 (11.8)	3 (8.3)	-	0.706*
Unsteadiness	2 (5.9)	6 (16.7)	-	0.266*
Somnolence	2 (5.9)	6 (16.7)	-	0.266*

* Fisher Exact test was used

Table 4. The effects of dense cranial electroacupuncture stimulation on platelet 5-HT parameters

Variable	Mean±SD value				
	Healthy controls (n=22)	Sham acupuncture (n=34)		Dense cranial electroacupuncture stimulation (n=36)	
		Baseline	Week 2	Baseline	Week 2
Platelet					
Serotonin type 2A receptors	1.3±0.2	2.6±1.5*	2.5±1.5	2.6±1.5*	2.5±1.5
Serotonin transporter	1.6±0.2	2.3±1.5	2.0±1.5	2.2±1.8	2.1±1.8
5-HT (ng/10^9)	527.2±111.1	81.8±92.8*	81.6±91.8	84.3±62.2*	87.0±74.2
5-hydroxyindoleacetic acid (ng/10^9)	632.9±214.6	192.3±129.0*	231.7±196.1	215.2±149.5*	249.6±203.3
Turnover	0.9±0.3	0.7±1.2	0.7±0.7	0.6±0.6	0.6±0.6
Platelet-poor plasma					
5-HT (ng/ml)	9.3±1.6	4.8±1.5*	5.3±1.2	5.5±2.3*	5.4±2.4
5-hydroxyindoleacetic acid (ng/ml)	10.4±2.3	6.7±2.9*	7.5±3.6	7.0±3.0*	7.1±3.3
Turnover	1.0±0.3	0.8±0.5	0.8±0.4	0.9±0.4	0.9±0.5

* vs. healthy controls, P<0.01, one-way analysis of variance

benefits of DCEAS were derived from placebo effects.

There were several limitations in the present study. First, most subjects were females. There may be gender- and ethnic-differences in acceptance and credibility of acupuncture, suggesting a form of demographic bias. Single-blind treatment allocation might lead to effects mediated by the non-blind acupuncturists. Second, DCEAS only achieved a clinically meaningful (but not significant) difference in terms of the response rate (DCEAS: 19.4% vs. sham: 8.8%). This may be related to the relatively short-term (3-week) treatment. Long-term studies of antidepressant efficacy of DCEAS are warranted. Finally, no significant changes in platelet 5-HT parameters (baseline

to post-treatment) were noted in DCEAS-treated patients, suggesting that DCEAS may have minimal effects on platelet 5-HT systems. Evaluation of DCEAS effects on the brain 5-HT neuronal system may provide insight into central mechanisms responsible for the antidepressant effects of DCEAS. Several baseline 5-HT parameters of depressed patients differed significantly from those of healthy controls, and correlated significantly with the severity of depression symptoms. The platelet 5-HT indices seem to be potential biomarkers, reflecting the clinical status of major depression, although they are not directly involved in the physiopathology of major depression.

Implications

As patients with moderate and severe major depression have a higher risk of suicide and symptom worsening in the early phase of SSRI treatment, DCEAS can be an additional therapy. Neurobiological mechanisms responsible for DCEAS effects may warrant further investigation using neuroimaging approaches.

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