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REGULAR ARTICLE

Multicenter randomized controlled trial of bifrontal, bitemporal, and right unilateral electroconvulsive therapy in major depressive disorder

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Aim: Electroconvulsive therapy (ECT) has been shown to be the most effective and rapid treatment for severe depression. Electrode placement is one of the most important factors that affect ECT's efficacy and side-effects profile. Bifrontal, bitemporal, and unilateral are the three most used electrode placements. Very few studies have directly compared the efficacy and cognitive side-effects of the three placements. The aim of this study was to compare the efficacy and cognitive side-effects associated with bifrontal, bitemporal, and unilateral electrode placements.

Methods: This multicenter randomized, blinded, controlled trial included 40 patients in each of the three groups. Most of the patients (94.8%) completed six ECT treatments. We used mixed-model analyses to compare differences in 17-item Hamilton Depression Rating Scale (HAMD-17) and Clinical Global Impression (CGI) scores among the three groups and the five times series (baseline, Week 1, Week 2, Week 3, and Week 4). The cognitive outcome was Mini-Mental State Examination (MMSE) score.

Results: HAMD-17 and CGI scores did not differ significantly across the groups (HAMD-17 scores: $z = -1.13$, $P = 0.259$; CGI scores: $z = -0.35$, $P = 0.729$). MMSE scores at pre- and post-ECT were similar across the three groups ($F = 2.06$, $P = 0.133$). However, subgroup analysis using paired t-tests showed that MMSE scores improved in the right unilateral and bifrontal groups ($t = 2.745$, $P = 0.0098$; $t = 2.464$, $P = 0.0204$), but did not change in the bitemporal group ($t = 1.188$, $P = 0.2461$).

Conclusion: The efficacy of right unilateral and bifrontal ECT placement was similar to that of bitemporal ECT. The physical side-effects were also similar across the three groups. Right unilateral and bifrontal ECT placement were associated with improved cognitive outcomes, but bitemporal ECT placement was not.

Keywords: *cognitive function, efficacy, electroconvulsive therapy, electrode placement, major depressive disorder.*

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Major depressive disorder (MDD) is a highly prevalent (6%) mental illness in China.[1] Given that China has such a large population and that MDD can impair the quality of life and lead to death by suicide, rapid and effective treatment for MDD in China is very important.

Although antidepressant medications are effective for the majority of patients,[2] many depressive patients exhibit severe syndromes by the time they present at hospital[3] because they have not received timely treatment. This lack of treatment-seeking behavior may be due to the patient's lack of knowledge or negative attitude toward mental illness, or an inability and unwillingness of general physicians and primary-care health workers to provide basic psychiatric services in China because they have little or no training in mental health.[1]

Electroconvulsive therapy (ECT) has been shown to be the most effective and rapid treatment for severe depression[4] though it is still not widely accepted by the general population because of side-effects, such as nausea, headache, jaw pain or muscle ache, and various cognitive deficits.[5] However, new techniques, such as ultrabrief right unilateral ECT, have shown fewer cognitive side-effects.[6]

Other factors, for example anesthesia medicines,[7,8] treatment frequency (twice or thrice weekly)[9] and electrode placements, may be associated with variable ECT outcomes. Electrode placement is one of the most important factors that affect efficacy and the side-effects profile of ECT treatment.[5,10–12] Bifrontal, bitemporal, and unilateral are the three most used electrode placements and the UK ECT Review Group reported that bilateral electrode placement was moderately more effective than right unilateral placement.[13] However, a later meta-analysis reported similar efficacy among bifrontal, bitemporal, and unilateral placements.[14] Several other studies have reported no difference in efficacy between high-dose right unilateral ECT and bilateral ECT,[15] and some studies have indicated that unilateral electrode placement on the right side is associated with a lower incidence of cognitive side-effects.[3,14,16,17]

While Dunne and McLoughlin's meta-analysis found that bifrontal and bilateral ECT are equally efficacious, as are bifrontal and right unilateral ECT,[14] only two studies have directly compared both the efficacy and cognitive side-effects of these three placements. The relative efficacy of the three ECT electrode placements is thus still unclear. In this study, we aimed to explore the efficacy and

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This trial was registered with clinicaltrial.gov (No. NCT02066077).

physical and cognitive side-effects of these placements in the acute treatment phase in Chinese MDD patients. We hypothesized that bifrontal, bitemporal, and unilateral placements would be similarly efficacious, but that bitemporal placement would be associated with greater cognitive side-effects.

Methods

Study design and participants

This was a randomized, rater-blinded, parallel, five-center, three-arm trial (Register No.: NCT02066077 in clinical trial.gov). Participants were MDD outpatients or inpatients recruited in five hospitals between January 2014 and July 2016. Inclusion criteria were that eligible participants were: more than 18 years old, met diagnostic criteria for MDD in the DSM-IV-TR (Chinese edition of the Mini-International Neuropsychiatric Interview[18] and total score for the 17-item Hamilton Depression Rating Scale [HAMD-17] was more than 17[19]), and were referred for ECT.

Exclusion criteria were that patients: were unfit for general anesthesia or ECT; had been treated with ECT within the last 6 months; or had a history of schizophrenia, schizoaffective disorder, neurodegenerative disorder, or alcohol/substance abuse. The number of ECT sessions (maximum = 12) was determined by referring clinicians in consultation with patients. This study was approved by the Shanghai Mental Health Center research ethics committee. Participants and families gave written informed consent before the screening process.

After baseline assessments and screening and before the first ECT session, patients were randomized (1:1:1) to the bifrontal, bitemporal, or unilateral ECT groups using the computer program STATA (StataCorp, College Station, TX, USA). The evaluator remained blind to patient allocation.

Procedure

Brief-pulse (1.0-ms pulse width; current amplitude 800mA) ECT was administered thrice weekly, using propofol (1.0–1.5 mg/kg) anesthesia, and succinylcholine (0.5 mg/kg–1.0 mg/kg) for muscle relaxation.[4] Seizure threshold was established by dose titration at the first session.[4] Subsequent treatments were 1.5 × threshold for bitemporal and 6 × threshold for unilateral (d'Elia placement) ECT. Stimulus charge was titrated upward as required during the treatment course. Patients continued regular antidepressants, such as SSRIs. The side-effects of nausea, headache, and muscle aches were recorded on the last ECT treatment session, mostly at Week 4 (ECT treatment session 12). Serious adverse events that required prolonged medical attention or were life-threatening were recorded.

Outcome

The primary and secondary depression severity outcomes were total scores on the HAMD-17 and the Clinical Global Impression (CGI)[20] which were administered at baseline, Week 1 (after three ECT treatments), Week 2 (after six ECT treatments), Week 3 (after nine ECT treatments), and at the completion of the ECT course. The cognitive outcome was the Mini-Mental State Examination (MMSE) score.[21] In the trial registration, the Wechsler Memory Scale (WMS) was a specified outcome measure. However, in piloting the study we found that severely depressed patients had difficulty with the WMS due to inhibition of thought, which resulted in them needing a very long time to complete the scale. We therefore made the pragmatic decision to adjust the battery of psychological tests by substituting the MMSE for the WMS for the trial. Standardized measures of global cognition MMSE were collected at baseline and after the last ECT treatment. Baseline assessments also included collection of demographic variables (age, sex, illness duration, education degree, family history, and previous inpatient admissions).

Statistical analysis

We estimated that 33 patients were required in each of the three groups to have 81.6% power, using two-sided, repeated-measures (repetitions = 5), F-tests (three groups), within factors, F-test at 5% level.[22] We used STATA (version 11) for statistical analyses. The primary statistical analysis was assessment of difference in HAMD-17 scores among the three groups from baseline to Week 4 (the end of treatment). Analyses were on the intention-to-treat principle. Handling of missing data was based on standard methods in xtmixed in STATA,[23] which were analyzed using a mixed model to compare differences among the three groups and the five times series. We used the same approach to compare total CGI scores. The cognitive outcome was MMSE score (pre- and post-treatment comparison). We used χ^2 to compare differences in the adverse events proportions among the three treatment groups.

Results

Participant characteristics

We screened 382 patients, and 120 eligible and interested patients were randomized to the three groups. Forty MDD patients were assigned to each of the three electrode-placement groups as shown in the Consolidated Standards of Reporting Trials (CONSORT) diagram (Appendix S1 and Fig. 1).[24,25] One patient in each of the right unilateral ECT treatment group and bifrontal ECT treatment group, and two patients in the bitemporal ECT treatment group received fewer than the required number of treatments so their data were excluded from the analyses.

Baseline and demographic characteristics

There were no significant differences in age, sex, HAMD-17 and CGI severity, or MMSE scores among the three groups at baseline (see Table 1). The mean age of the total sample was 48.7 years (SD = 17.6), and 80% of the participants were female. Mean HAMD-17 score at baseline was 27.0 (SD = 4.8), and mean CGI score was 5.2 (SD = 0.9). On average, participants had experienced three previous episodes of MDD, and the median duration was 3 months. The total sample had similar characteristics to those in previous relevant trials.[4,10,11]

Anesthesia medications were the same and the doses were similar for the three groups (Table 2). Consistent with previous studies,[11] the threshold was lower in the bifrontal and bitemporal groups than in the right unilateral group, and seizure durations were similar among the three groups (Table 2). There was no significant difference among the groups for total number of ECT sessions ($X^2 = 0.312$, $P = 0.577$).

Primary and secondary mood outcomes

Nearly 94.8% (110/116) of all included patients completed nine ECT treatments and 78.4% (91/116) completed 12 treatments. There was no significant difference among the proportions of patients completing nine or 12 treatments across the three groups. Table 3 shows the total HAMD-17 scores before and after ECT treatment for the three groups. Mixed-model analyses using STATA 11 indicated no differences in mean total HAMD-17 scores for the three ECT groups at baseline, after three treatments (Week 1), six treatments (Week 2), nine treatments (Week 3), and 12 treatments (Week 4; $z = -1.13$; 95% confidence interval = −1.54 to 0.414; $P = 0.259$). Secondary mood outcomes of CGI scores were similar across three groups ($z = -0.35$, 95% confidence interval = −0.194 to −0.135; $P = 0.729$) as shown in Figure 2 and Table 3.

Cognitive outcomes

The cognitive outcomes, as assessed by MMSE scores at pre- and post-ECT, were similar across the three groups (among groups, $F = 2.06$, $P = 0.133$). Analyses using paired t-tests showed that MMSE scores were improved in the sample as a whole ($t = 3.786$, $P = 0.0003$). Within groups, analyses showed significantly elevated MMSE scores in the right unilateral and bifrontal groups ($t = 2.745$,

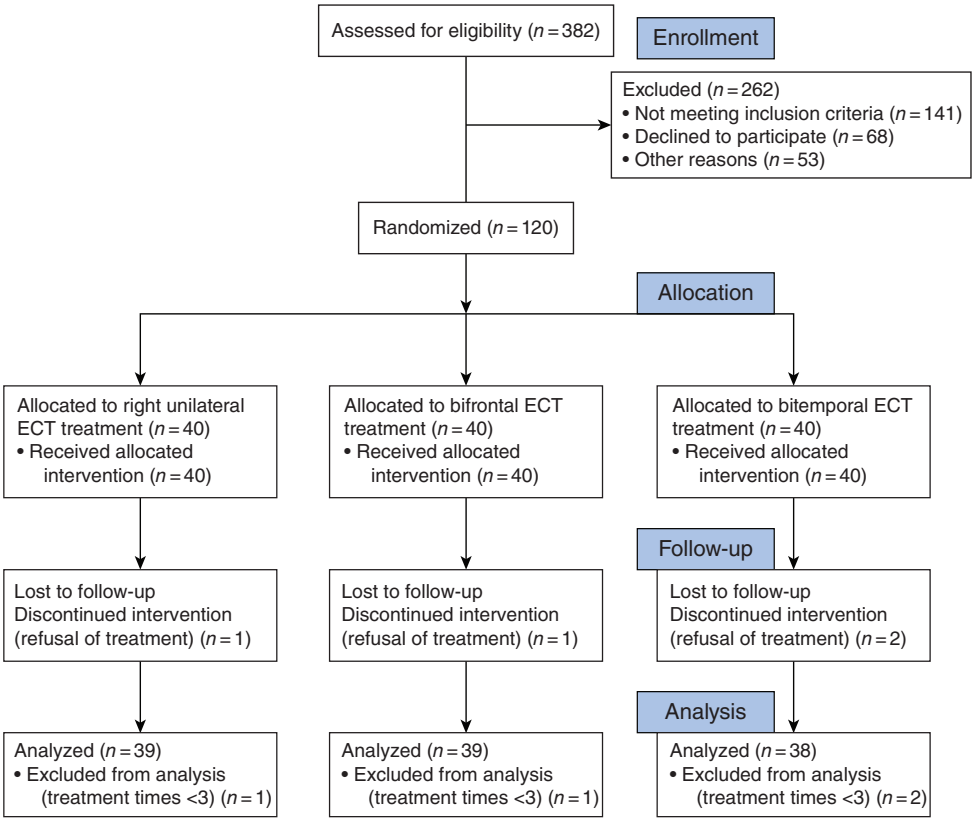

Fig.1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. ECT, electroconvulsive therapy.

$P = 0.0098$; $t = 2.464$, $P = 0.0204$), but the bitemporal group did not change ($t = 1.188$, $P = 0.2461$), as shown in Table 4 and Figure 3.

Adverse events

Generally, there were no differences between the three groups in regards to headaches ($X^2 = 0.851$, $P = 0.653$), nausea ($X^2 = 0.953$, $P = 0.621$), or muscle pain ($X^2 = 0.717$, $P = 0.699$). None of these events resulted in dropout.

Discussion

Main findings

Our findings show that the efficacy of thrice-weekly ECT was similar for three commonly used treatment sites: the right unilateral, bifrontal, and bitemporal. Thrice weekly is the regular treatment frequency and the three treatment sites are common in regular clinical practice[26] that includes continued antidepressant pharmacotherapy. The results of our study support the recent finding by Semkovska *et al*. that twice-weekly high-dose unilateral ECT is not inferior to bitemporal ECT for severe depression.[4] This suggests that efficacy among the three treatment sites is similar regardless of the frequency (twice or thrice weekly) of ECT treatment.

Findings from other studies

Previous studies show that ECT treatment is more efficient thrice weekly than twice weekly[9,13] and that anesthesia medicines can also affect duration of seizure in ECT treatment.[7,27] However, all of the patients in our study received thrice-weekly ECT and received the same anesthesia medicine (propofol) in order to avoid bias in treatment frequency and anesthesia medicine. Overall, our findings for the

Table 1. Baseline clinical and demographic characteristics

	Total ($N = 116$)	Right unilateral ($n = 39$)	Bifrontal ($n = 39$)	Bitemporal ($n = 38$)	P value among three groups
Age (years)	48.7 ± 17.6	52.1 ± 18.5	45.9 ± 14.9	48.2 ± 18.9	0.493
Sex (M/F)	22/94	8/31	7/32	7/31	0.954
Duration of education (years)	11.8 ± 3.4	11.9 ± 3.4	11.8 ± 2.9	11.8 ± 3.9	0.843
Episode duration (months, median)	3	3	3	2	0.314
No. of hospitalizations (median)	1	1	1	1	0.371
No. of previous episodes (median)	2	2	2	2	0.725
HAMD-17 score	27.0 ± 4.8	28.1 ± 5.4	27.0 ± 4.8	26.1 ± 4.1	0.914
CGI score	5.2 ± 0.9	5.3 ± 1.1	5.2 ± 0.7	5.2 ± 0.8	0.912
MMSE score	27.2 ± 4.5	26.8 ± 4.7	26.8 ± 5.5	28.1 ± 3.2	0.334

CGI, Clinical Global Impression; HAMD-17, 17-item Hamilton Depression Rating Scale; MMSE, Mini-Mental State Examination.

Table 2. Electroconvulsive therapy treatment characteristics

Variables	Total (N = 116)	Right unilateral (n = 39)	Bifrontal (n = 39)	Bitemporal (n = 38)	P-value among three groups
Anesthesia	1.0–1.5 mg/kg				
Succinylcholine	0.5–1.0 mg/kg				
Threshold		6×	1.5×	1.5×	
Completed proportion of three times	113 (97.4%)	37	39	37	0.361
Completed proportion of six times	110 (94.8%)	35	39	36	0.316
Completed proportion of nine times	91 (78.4%)	34	30	27	0.219
Completed proportion of 12 times	45 (38.8%)	16	11	18	0.212

Table 3. Clinical outcomes of HAMD-17 and CGI scores[†]

		Right unilateral (n = 39)	Bifrontal (n = 39)	Bitemporal (n = 38)	Total (N = 116)
HAMD-17 score	Baseline	28.1 (5.4) N = 39	27.0(4.8) N = 39	26.1(4.1) N = 38	27.0(4.8) N = 116
	Week 1	18.4 (6.7) N = 37	19.2(6.1) N = 39	16.4(5.6) N = 37	18.0(6.2) N = 113
	Week 2	10.7 (5.9) N = 35	12.7(6.4) N = 39	10.2(5.2) N = 36	11.2(5.9) N = 110
	Week 3	6.8 (5.0) N = 34	8.7(5.9) N = 34	7.0(4.7) N = 27	7.5(5.3) N = 91
	Week 4	5.0 (5.5) N = 16	8.5(6.6) N = 16	4.6(3.2) N = 18	5.7(5.1) N = 45
CGI score	Baseline	5.3 (1.1) N = 39	5.2(0.7) N = 39	5.2(0.7) N = 38	5.2(0.9) N = 116
	Week 1	4.1 (1.1) N = 37	4.1(0.8) N = 39	3.9(1.0) N = 37	4.0(1.0) N = 113
	Week 2	2.9 (1.2) N = 35	3.0(0.9) N = 39	2.7(0.8) N = 36	2.9(1.0) N = 110
	Week 3	1.9 (1.1) N = 34	2.5(0.9) N = 30	2.1(1.0) N = 27	2.1(1.0) N = 91
	Week 4	1.5 (1.3) N = 16	2.2(0.8) N = 11	1.7(0.8) N = 18	1.7(1.0) N = 45

[†]There were no significant differences among the three groups (HAMD-17 scores: z = −1.13; 95% confidence interval = −1.54 to 0.414; P = 0.259; CGI scores: z = −0.35; 95% confidence interval = –0.194 to −0.135; P = 0.729, respectively) using mixed effects method.
[a] CGI, Clinical Global Impression; HAMD-17, 17-item Hamilton Depression Rating Scale.

primary and secondary outcomes (HAMD-17 and CGI scores) show that the efficacy of ECT for treating depression was similar in the three treatments sites. Our study supports the research suggesting that all of the three ECT treatment sites are useful in clinical practice.[9,28]

Investigation of the cognitive side-effects revealed that MMSE scores were higher after ECT treatment in the sample as a whole, and in the right unilateral and bifrontal subgroups. However, MMSE scores did not change in the bitemporal treatment group. Although the MMSE was used to assess global cognitive functioning, its ability to assess the cognitive side-effects of ECT is limited[5,29] because it does not assess domains of cognitive functioning.[30] Despite this, and in line with previous studies,[10,11,14,15] our results suggest that bitemporal ECT treatment might influence cognitive functioning more than either right unilateral or bifrontal ECT treatment, which are both associated with improved cognitive functioning. The proportions of common physical side-effects, such as headaches, nausea, and muscle pain, were similar in the three groups, which is also in line with previous studies.[5,13,16]

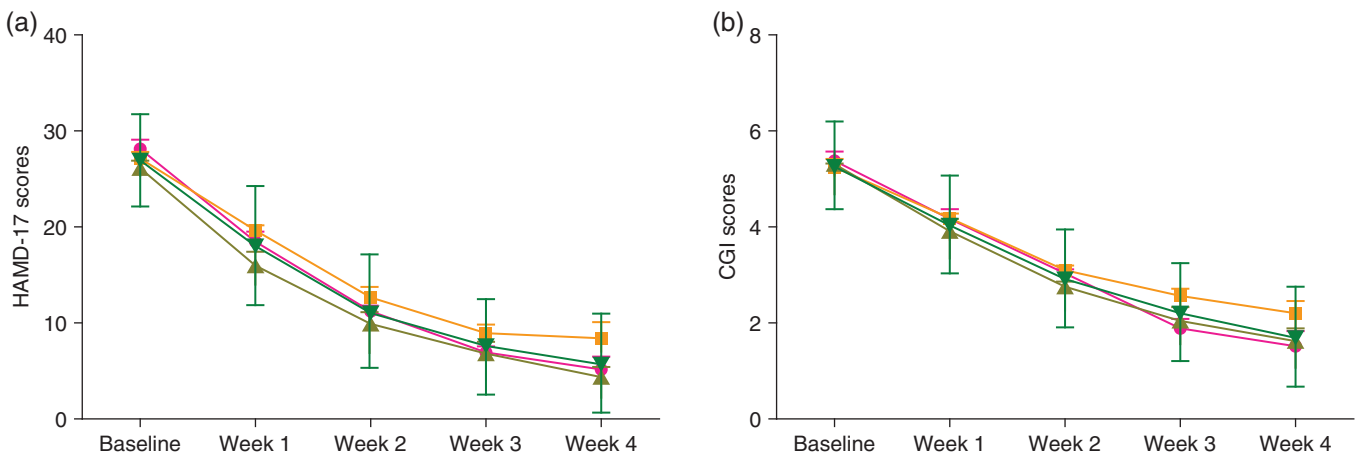

Fig.2 Changes in the (a) 17-item Hamilton Depression Rating Scale (HAMD-17) scores and (b) Clinical Global Impression (CGI) scores according to electrode placement group. (—●—) Right unilateral group. (—■—) Bifrontal group. (—▲—) Bitemporal group. (—▼—) Total.

Table 4. Summary statistics table of MMSE scores among the three groups[†]

Variables	Right unilateral (n = 39)	Bifrontal (n = 39)	Bitemporal (n = 38)	Total (N = 116)
Baseline MMSE scores	26.8 ± 4.7	26.8 ± 5.5	28.1 ± 3.2	27.2 ± 4.5
No. of samples	39	39	38	116
Endpoint MMSE scores	28.9 ± 1.4	28.7 ± 1.7	29.3 ± 1.3	28.9 ± 1.5
No. of samples	33	29	26	88

[†]Between-groups differences; there were no differences among the three groups in MMSE scores at pre- and post-ECT (F = 2.06, P = 0.133).
MMSE, Mini-Mental State Examination.

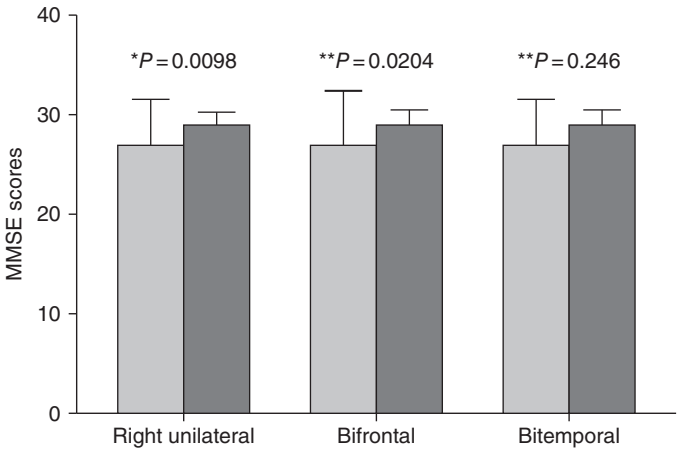

Fig.3 Within-group differences in Mini-Mental State Examination (MMSE) scores. (▨) Pre-electroconvulsive therapy. (▩) Post-electroconvulsive therapy.

Limitations

Our study has some limitations. First, each group was relatively small. However, our study design provided adequate statistical power for repeated measures, and the mixed model was useful for handling missing data as several patients had dropped out of each group by the follow-up phase.[23,31] Second, the MMSE is limited in terms of the assessment of cognitive functioning. Nevertheless, it is the most commonly used and available scale of cognitive functioning in clinical practice.[32] Though there is no statistical difference between the three groups in baseline MMSE, it seems that the bitemporal group had a slightly higher MMSE score at baseline. Thus, the comparison of cognitive function should be interpreted carefully. Finally, all trial participants were administered thrice-weekly ECT and this does not reflect routine practice in which treatment is limited to twice or thrice weekly according to the patient's condition. We used the same treatment frequency protocol to avoid this bias. Further studies should use larger samples and explore the interaction effect between different treatment sites and different treatment frequencies.

Implications

Our study has important clinical implications for the use of ECT for MDD. The efficacy of high-dose right unilateral and bifrontal ECT treatment was similar to that of bitemporal ECT, and the physical side-effects were similar across the three groups. However, bitemporal electrode placement in ECT has no impact on cognitive outcomes, whereas the other two placements are associated with improvements. Further studies should focus on the maintenance of the effectiveness of ECT at each site and the side-effects of different treatment sites and frequencies.

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Disclosure statement

The authors have no conflicts of interest to state.

Author contributions

Conceived and designed the experiments: Y.X. and D.M. Performed the experiments: L.S., Y.J. and S.L. Analyzed the data: L.S. and Y.X. Wrote the paper: All authors.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Consolidated Standards of Reporting Trials (CONSORT) checklist.