



ELSEVIER

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Low-charge electrotherapy for patients with schizophrenia: A double-blind, randomised controlled pilot clinical trial

Min-zhi Li^{a,†}, Li-chang Chen^{d,†}, Han Rong^a, Shu-xian Xu^{b,*,*}, Yi Li^a, Qi-fan Yang^b, Wen-feng Deng^b, He-zeng Yang^a, Xiao-ming Kong^e, Li Xiao^f, Xin-hui Xie^{a,c,e,*}

^a Department of Psychiatry, Shenzhen Kangning Hospital, Shenzhen, Guangdong, China

^b Department of Psychiatry, Second People's Hospital of Huizhou, Huizhou, Guangdong, China

^c Office of Science and Education, Second People's Hospital of Huizhou, Huizhou, Guangdong, China

^d Department of Biostatistics, School of Public Health, Southern Medical University, Guangzhou, China

^e Department of Psychiatry, Anhui Mental Health Center, Hefei, Anhui, China

^f Key Laboratory of Intelligent Information Processing, Advanced Computer Research Center, Institute of Computing Technology, Chinese Academy of Sciences, Beijing, China

ARTICLE INFO

Key words:

Low-charge electrotherapy
Electroconvulsive therapy
Schizophrenia
Adverse event
Double-blind
Randomised pilot trial

ABSTRACT

A double-blind, randomised controlled pilot clinical trial was conducted to assess the potential effectiveness and safety of low-charge electrotherapy (LCE) for patients with schizophrenia. Bitemporal LCE (approximately 2.8 Joules) was administered three times a week. The Positive and Negative Syndrome Scale score was set as the outcome measure. Any adverse event (AE) was recorded. Three visits occurred at baseline, post-treatment, and after one month of follow-up. Twelve patients were randomised to the electroconvulsive therapy (ECT) group or LCE group (6 patients in each group). No patient withdrew during the study. The LCE group did not experience seizures during the trial. Patients in both groups showed significant improvements in clinical measures after treatment, and the reduction of all scale scores between the two groups was nonsignificant. The LCE group experienced significantly fewer AEs than the ECT group. Compared with ECT, LCE exerts similar antipsychotic effects while causing fewer AEs. Thus, LCE has the potential to be a safe and effective treatment for patients with schizophrenia, but further research is needed.

1. Introduction

Worldwide, schizophrenia (SCZ) is one of the most severe mental health problems. Routine first-line treatments, such as antipsychotics, are insufficient, and approximately 20–30% of patients fail to respond to first-line treatments (Dold and Leucht, 2014). Based on accumulating evidence, the administration of electroconvulsive therapy (ECT) along with antipsychotic medication is highly effective for patients exhibiting treatment resistance and when a rapid response is required (Bansod et al., 2018; Kristensen et al., 2013; Pompili et al., 2013; Tharyan and Adams, 2002, 2005; Zheng et al., 2016). Additionally, the combination of clozapine with ECT is a safe and effective treatment option for patients with SCZ who fail to respond to clozapine (Grover et al., 2017; Lally et al., 2016; Petrides et al., 2015).

ECT has been used for decades and is considered a treatment for

major depression and bipolar disorder. However, the use of ECT to treat SCZ is highly variable worldwide (McCall, 2010; Teh et al., 2005). Additionally, ECT has rarely been used to treat SCZ in western countries for decades (Leiknes et al., 2012). In recent years, interest in ECT has been renewed, particularly for the treatment of medication-resistant SCZ (Leiknes et al., 2012; Tharyan and Adams, 2005). Despite the demonstrated effectiveness of ECT for psychotic symptoms, its use is limited due to adverse events (AEs), such as headache, disorientation, nausea, tiredness, and muscle pains, particularly memory complaints (Kristensen et al., 2011; Tor et al., 2017). These side effects may be affected by the ECT dose, induced seizures or bitemporal electrode placement (Sackeim et al., 2008; Tor et al., 2017). Thus, the goal of reducing the side effects of ECT while maintaining its efficacy is very attractive to researchers.

The mechanism of ECT remains poorly understood, particularly

* Corresponding author at: 1. Department of Psychiatry, Shenzhen Kangning Hospital, Shenzhen, Guangdong, China; 2. Department of Psychiatry, Second People's Hospital of Huizhou, Huizhou, Guangdong, China; 3. Office of Science and Education, Second People's Hospital of Huizhou, Huizhou, Guangdong, China.

** Corresponding author.

E-mail addresses: shuxianxu@outlook.com (S.-x. Xu), xxh.med@gmail.com, xin-hui.xie@live.com (X.-h. Xie).

† The first two authors contributed equally to this paper.

<https://doi.org/10.1016/j.psychres.2018.12.143>

Received 17 September 2018; Received in revised form 16 December 2018; Accepted 28 December 2018

Available online 28 December 2018

0165-1781/ © 2018 Elsevier B.V. All rights reserved.

with regard to its antipsychotic effects (Rosenquist et al., 2014; Sackeim, 2015). One widespread hypothesis is that a seizure must undoubtedly be induced to achieve the therapeutic effect of ECT; therefore, the natural aim is to induce maximal seizure activity using minimal electrical energy (Sackeim et al., 1987; Small et al., 1968). However, we found an interesting phenomenon after reviewing some articles. Some ECTs that fail to induce seizures (i.e., subthreshold seizures) exert antidepressant effects and no obvious side effects (Alexander, 1950; Androp, 1941; Beran et al., 1952; Olkon, 1957; Prudic et al., 1994). Notably, a recent open-label, proof-of-concept study reported significant antidepressant effects of nonconvulsive electrotherapy (NET, approximately 2.6 Joules (J)) or low-charge electrotherapy (LCE) that are similar to ECT, but without serious AEs (particularly a lack of cognitive AEs) (Regenold et al., 2015). Some authors have also suggested that the antidepressant effect of rTMS implies that seizure induction may not be necessary for the antidepressant effect of ECT (Post et al., 1997). However, a relevant NET or LCE study of patients with SCZ has not been conducted. Considering the potential benefits of LCE, we designed the present double-blind, randomised controlled pilot clinical trial to examine the feasibility of using LCE to treat patients with SCZ.

To our knowledge, this study is the first to assess the efficacy and safety of LCE for patients with SCZ. We used the standard ECT technique but set the LCE charge to approximately 2.8 Joules, without inducing seizures. Our hypothesis was that LCE also exerts antipsychotic effects while causing fewer adverse cognitive effects than ECT.

2. Methods

Our study was conducted in accordance with the Declaration of Helsinki, and the Shenzhen Kangning Hospital Ethics Committee approved our plan. Inpatients were recruited from the Shenzhen Kangning Hospital at Shenzhen city, Guangdong, China.

2.1. Participants

The following inclusion criteria were established: 1. $18 \leq \text{age} \leq 60$ years, 2. inpatients diagnosed with SCZ according to the DSM-5 with SCID-5, 3. a poor response to at least one month of an appropriate and stable dose of first-line antipsychotic treatment (such as risperidone, aripiprazole, quetiapine, or olanzapine), and 4. a current Positive and Negative Syndrome Scale (Kay et al., 1987) (PANSS) score ≥ 65 . The exclusion criteria were: 1. the presence of other comorbid mental disorders; 2. a history of psychoactive substance abuse; 3. a history of stroke, epilepsy or severe cardiovascular disease; 4. the presence of severe affective symptoms or suicidal ideas (because ECT exhibits significant efficacy for affective symptoms, we cannot distinguish the improvement in psychotic symptoms caused by ECT/LCE or associated improvements in affective symptoms); 5. a history of TMS or ECT treatments within the previous 6 months; 6. a history of allergies to anaesthesia; 7. pregnancy; and 8. unwilling to provide a detailed address or refusal to participate in follow-up studies. Please see Fig. 1 for the flow diagram.

2.2. Sample size calculation

Because this investigation was a pilot study and results from similar clinical trials were not available to calculate the sample size, we set the sample number to 6 patients per group.

2.3. Randomisation and blinding methods

All patients were randomised using a computer-generated randomisation sequence (the test group was the LCE group and the control group was the ECT group). The researcher who generated the randomisation sequence and the ECT instrument operator did not participate

in the clinical evaluations of the patients. After each ECT/LCE procedure, the instrument operator reset the parameters of the ECT equipment to prevent other operators from detecting the group to which the patient belonged. Treatment status was concealed from the patients and psychiatrist who performed the clinical assessments.

2.4. ECT/LCE treatment procedures

ECT or LCE was administered with a spECTRUM 5000Q ECT Instrument (MECTA Corporation, OR, USA) three times per week (Monday, Wednesday, and Friday). The energy of the LCE group was set to the minimum (2.8 J) with a stimulus duration = 0.5 s and a frequency = 20 Hz. The energy of the ECT group was set using the half-age strategy (Petrides et al., 2009; Petrides and Fink, 1996) with a stimulus duration = 1–6 s and frequency = 50–70 Hz. The pulse width was set to 1 ms and current was set to 800 mA for both groups. Patients were administered etomidate anaesthesia. Succinylcholine and atropine were used to relax the muscles and suppress gland secretions during each treatment session. Bipolar ECT/LCE electrodes were placed on each patient, and seizure activity was monitored with electroencephalography using the ECT instrument. The maximum number of ECT/LCE sessions was 12, and the patient could terminate the ECT/LCE procedure at any time. The patient's psychiatrist decided whether the patient terminated ECT/LCE (the patient's doctor did not know the patient's group). After the ECT/LCE sessions, the patient continued to take the original treatment medication. Patients could withdraw from the trial at any time.

2.5. Pharmacotherapy augmentation strategies

Patients in both groups maintained their antipsychotic medications before the start of and throughout the trial. Anti-convulsant drugs or mood stabilisers were discontinued during ECT/LCE. Patients exhibiting agitation were temporarily administered haloperidol injections or benzodiazepine injections, but the use of benzodiazepines was prohibited 24 h before the assessment. Patients were allowed to take a single dose of alprazolam when they felt anxious (but discontinued the drug within 15 h before ECT/LCE); other antipsychotics were banned during the study. For a detailed description of pharmacotherapy, please see the supplemental materials.

2.6. Clinical measures

The clinical status was measured at baseline, after the last ECT/LCE session and one month after the last ECT/LCE session. The mean change in the total PANSS (Kay et al., 1987) total score from baseline (visit 1) to the last ECT/LCE session (visit 2) was used as the primary outcome measure. The mean changes in scores for PANSS subscales (PANSS Positive scale (PANSS-P), Negative scale (PANSS-N) and general psychopathology scale (PANSS-G)) between visits 1 and 2 were used as the secondary measures. Any adverse event (AE) was recorded to analyse the safety of ECT/LCE.

2.7. Statistical analyses

Demographic and baseline data were analysed using independent two-sample *t*-tests or Chi-square and Fisher's exact tests. All analyses of the primary and secondary measures and safety indicators were performed in the modified intent-to-treat population (MITTP) (at least one treatment and at least one post-baseline measure). For the primary and secondary indicators, we used independent two-sample *t*-tests as the main analysis and mixed-effects model repeated measures (MMRM) as the supplementary analysis. The safety indicators were analysed with Chi-square/Fisher's exact tests. The significance level was set to 0.05 (two tailed). All statistical analyses were performed with SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

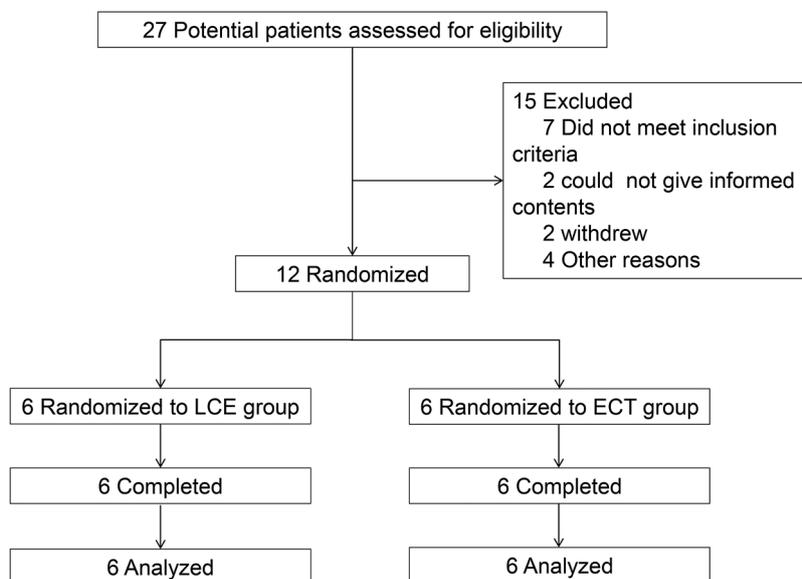


Fig. 1. Flow chart. ECT = electroconvulsive therapy; LCE = low-charge electrotherapy.

3. Results

3.1. Baseline characteristics

All 12 inpatients were recruited from November 1st 2016 to December 30th 2017. Please see Table 1 for baseline characteristics. The PANSS-G scores of the LCE group were somewhat higher than the scores of the ECT group.

3.2. Study procedure

No participant withdrew during the study. All subjects completed the ECT/LCE procedures with no drop-outs. The number of ECT/LCE treatments administered to each group was 7.5 ± 1.8 in the ECT group and 8.0 ± 3.1 in the LCE group ($t = -0.344, p = 0.738$). Patients in the LCE group did not experience seizures during the trial, while patients in the ECT group had episodes of seizures during each trial. The average energy, charge, frequency, stimulus duration and seizure duration values for the ECT group were 28.3 ± 9.4 J, 160.7 ± 53.3 mC, 58.3 ± 5.0 Hz, 1.7 ± 0.5 s, and 70.5 ± 23.0 s, respectively. The

Table 1
Baseline characteristics.

Characteristics	ECT group (Mean \pm SD)	LCE group (Mean \pm SD)	t	p
Age	39.3 \pm 12.0	32.7 \pm 9.4	1.073	0.309
Male/female ^a	0/6	1/5	-	1.000
Education year	10.2 \pm 5.1	10.8 \pm 4.9	-0.232	0.821
Onset of disease	31.8 \pm 11.3	28.7 \pm 10.0	0.515	0.618
Disease course	7.4 \pm 6.8	5.3 \pm 3.3	0.686	0.508
Medication ^a	6 of 6	6 of 6	-	1.000
ECT/LCE number	7.5 \pm 1.76	8.0 \pm 3.10	-0.344	0.738
Equivalent chlorpromazine dose	483.7 \pm 168.1	495.0 \pm 190.1	-0.108	0.916
PANSS Total	81.3 \pm 2.3	96.8 \pm 21.0	-1.793	0.132
PANSS-P	23.3 \pm 3.6	23.5 \pm 3.1	-0.087	0.933
PANSS-N	14.0 \pm 4.9	18.8 \pm 10.6	-1.010	0.346
PANSS-G	44.0 \pm 5.0	54.5 \pm 9.8	-2.341	0.041

PANSS = positive and negative syndrome scale; PANSS-P = PANSS positive scale; PANSS-N = PANSS negative scale; PANSS-G = PANSS general psychopathology scale; ECT = electroconvulsive therapy; LCE = low-charge electrotherapy; SD = standard deviation.

^a Fisher's exact tests.

initial doses of anaesthesia (etomidate) for the LCE and ECT group were 12.8 ± 2.1 mg and 11.7 ± 1.8 mg, respectively; the etomidate dose was not changed during LCE or ECT procedures. The initial dose of muscle relaxant (succinylcholine) administered to the LCE and ECT group was 61.7 ± 10.8 mg and 53.3 ± 8.8 mg, respectively, and the succinylcholine dose was not changed during ECT procedures. However, the succinylcholine dose administered to three patients in the LCE group was reduced, and as a result, the ending dose of succinylcholine of LCE group was 57.5 ± 10.4 mg. All patients completed the clinical assessments at all three visits.

3.3. Clinical outcomes

Patients in both groups showed significant improvements in clinical measures after ECT/LCE procedures. In the comparison of the baseline and post-ECT/LCE time points, the reduction in the PANSS, PANSS-P, PANSS-N, and PANSS-G scores between the two groups was non-significant ($t = -1.06, p = 0.316$; $t = -0.86, p = 0.409$; $t = -0.74, p = 0.479$; and $t = -1.10, p = 0.298$, respectively). Table 2 shows the detailed comparisons of PANSS scores, the scores on the three subscales and effect sizes (using Hedges' g and its 95% confidence interval); the reduction in differences in total PANSS and subscale scores between the two groups was nonsignificant. Table 3 shows the estimated clinical characteristics based on the MMRM (baseline PANSS-N score as a covariate). The group*time interaction was nonsignificant and was not included in the final model. Time exerted a significant effect on the PANSS total and subscale scores, but the between-group effects were nonsignificant, except for PANSS-G scores. Fig. 2 shows the changes in PANSS scale scores over time. Supplemental material sFigure 1 shows the changes in PANSS scale scores of each participant over time.

3.4. Adjunct drug use

Please see supplemental materials Table 1.

3.5. AEs

In the ECT group, 15 AEs were recorded for 5 patients receiving 45 ECTs versus 2 AEs for 2 patients receiving 48 LCEs. The difference in the number of patients experiencing AEs (5/6 versus 2/6) between the two groups was nonsignificant (Fisher's exact test, $p = 0.242$), while the difference in the number of AEs was significant between the two groups

Table 2
Comparisons of reduction of PANSS and three subscales and the effect sizes between baseline and post-ECT/LCE.

Measures	ECT group (Mean ± SD)	Hedges's g (95% CI)	LCE group (Mean ± SD)	Hedges's g (95% CI)	Differences between groups (95% CI)	t	p
PANSS Total score	28.2 ± 12.8	1.36 (−0.49, 3.21)	43.8 ± 34.0	1.76 (−0.49, 4.02)	−15.7 (−48.7, 17.4)	−1.06	0.3158
PANSS-P	10.5 ± 4.5	2.55 (0.60, 4.51)	12.8 ± 4.9	1.09 (−0.01, 2.19)	−2.3 (−8.4, 3.7)	−0.86	0.4094
PANSS-N	0.0 ± 6.2	0.00 (−1.15, 1.15)	5.0 ± 15.4	1.85 (−0.58, 4.28)	−5.0 (−20.1, 10.1)	−0.74	0.4786
PANSS-G	17.7 ± 9.4	1.93 (−0.44, 4.31)	26.0 ± 16.0	1.77 (−0.50, 4.04)	−8.3 (−25.2, 8.6)	−1.10	0.2978

PANSS = positive and negative syndrome scale; PANSS-P = PANSS positive scale; PANSS-N = PANSS negative scale; PANSS-G = PANSS general psychopathology scale; ECT = electroconvulsive therapy; LCE = low-charge electrotherapy; SD = standard deviation; CI = confidence interval.

(Chi-square value = 13.227, $p < 0.001$). For a detailed description, please see Table 4.

4. Discussion

All patients in this trial achieved improvements as measured by the scores on the PANSS-P and G subscales. The therapeutic effects of LCE and ECT were similar. Notably, the LCE group experienced significantly fewer side effects than the ECT group.

To our knowledge, this LCE study is the first to assess patients with SCZ. Based on the results, LCE may be a potential alternative treatment for SCZ. In the present trial, the mean effect sizes of the PANSS total scores measured using Hedges' g for the ECT and LCE groups were approximately 1.36 and 1.76, respectively, similar to other ECT trials (Lally et al., 2016; Petrides et al., 2015; Tharyan and Adams, 2005). The mean reduction in the scores recorded by both groups for the PANSS-P, PANSS-N, and PANSS-G scales was similar. However, in contrast to the ECT group, the LCE group was treated with only 2.8 J of energy per session without producing a seizure. This difference led us to question the necessity of inducing seizures and using a high power, which may also be related to serious side effects.

A generalised seizure has been considered a necessary condition for the efficacy of ECT since its introduction in 1938 (Kalinowsky and Hoch, 1946; Sackeim, 2015). Some studies reported significant correlations between measures of seizure expression and ECT efficacy (Nobler et al., 1993; Ottosson, 1960b; Ulett et al., 1956). Cronholm and Ottosson performed a trial (Ottosson, 1960b) comparing ECT to ECT

with a limited seizure duration in subjects with depression. Compared with the control groups, the group with reduced seizure durations required more treatments and the treatments exhibited less therapeutic efficacy. However, Regenold et al. argued that the study showed a positive relationship between antidepressant efficacy and seizure duration but could not prove that a seizure was necessary for ECT due to the lack of subthreshold stimulation (Regenold et al., 2015).

According to Regenold and colleagues, the therapeutic effect of no seizure electrotherapy on treatment-resistant major depressive disorder was similar to ECT (Regenold et al., 2015). As shown in the present study, NET or LCE may also be useful for patients with SCZ. This finding may be related to the electrode placement and action site; all patients in these two trials (Regenold et al., 2015) received transcranial electrode placements. Bilateral ECT causes haemodynamic changes in the bilateral prefrontal cortex, and an asymmetric alteration has been reported for patients with SCZ, but not patients with mood disorders (Fujita et al., 2011). Furthermore, other treatments, such as tDCS and rTMS, affect this area and can produce antidepressant effects without producing a seizure. However, their effects are not as good as ECT due to their lower energy. Thus, we postulate that electrode placements and suitable currents play important roles in the antipsychotic effects.

However, high intensity stimulation also exacerbates the side effects of the intervention, with little impact on efficacy (Ottosson, 1960b; Tor et al., 2017). Compared with other electrical treatments, the energy of ECT (usually 10–100 J per session) is extremely high. For decades, the most common practice was to set the ECT electricity as high as possible to ensure that seizures were induced, but this practice increased the

Table 3
Estimated clinical characters based on the mixed-effects model repeated measures (MMRM).

Measures	Visit points	ECT group (Mean ± SD)	LCE group (Mean ± SD)	Between groups effect		Time effect		Differences between groups (95% CI)
				F	p	F	p	
PANSS Total	1 Baseline	81.3 ± 2.3	96.8 ± 21.0	2.68	0.116	21.91	<0.001	−7.1 (−16.1, 1.9)
	2 Post-ECT/LCE	53.2 ± 11.7	53.0 ± 17.5					
	3 Follow up	49.0 ± 15.3	47.8 ± 10.3					
PANSS-P	1 Baseline	23.3 ± 3.6	23.5 ± 3.1	1.41	0.249	61.38	<0.001	1.8(−1.4, 5.1)
	2 Post-ECT/LCE	12.8 ± 4.0	10.7 ± 5.2					
	3 Follow up	12.0 ± 4.4	8.3 ± 1.5					
PANSS-N*	1 Baseline	14.0 ± 4.9	18.8 ± 10.6	1.14	0.314	6.74	0.029	−2.5(−7.7, 2.8)
	2 Post-ECT/LCE	14.0 ± 3.7	13.8 ± 5.9					
	3 Follow up	10.7 ± 4.2	12.5 ± 4.3					
PANSS-G	1 Baseline	44.0 ± 5.0	54.5 ± 9.8	10.16	0.004	19.73	<0.001	−6.4(−10.6, −2.2)
	2 Post-ECT/LCE	26.3 ± 5.8	28.5 ± 8.3					
	3 Follow up	26.3 ± 7.4	27.0 ± 7.0					

The interaction effects of group*time were nonsignificant and not included in the final model. The time effects were significant on the PANSS total score and subscales, but the between-group effects were nonsignificant except for PANSS-G.

PANSS = positive and negative syndrome scale; PANSS-P = PANSS positive scale; PANSS-N = PANSS negative scale; PANSS-G = PANSS general psychopathology scale; ECT = electroconvulsive therapy; LCE = low-charge electrotherapy; SD = standard deviation; CI = confidence interval.

* Baseline PANSS-N score as a covariate.

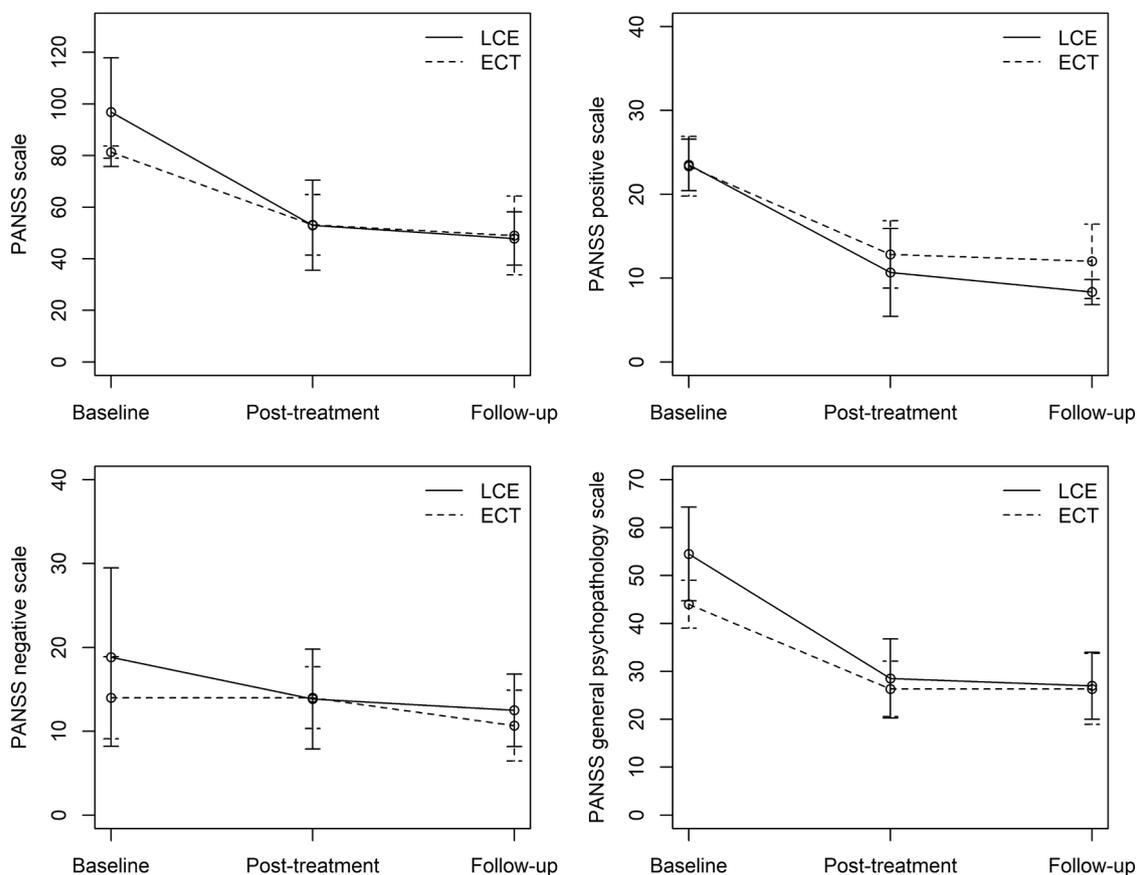


Fig. 2. Mean scores and standard deviations (SDs) for the PANSS and its three subscales (PANSS Positive scale (PANSS-P), Negative scale (PANSS-N) and general psychopathology scale (PANSS-G)) at each of the three visits.

Table 4
Adverse events in all patients.

AE	LCE group (6 patients, 48 LCEs)		ECT group (6 patients, 45 ECTs)	
	N of Patients ^a	N of AEs ^b	N of Patients ^a	N of AEs ^b
AE	2 (33.3%)	2	5 (83.3%)	15
Fever	1	1	1	2
Headache	1	1	4	5
Vomit	0	0	1	1
Disorientation	0	0	1	2
Subjective memory complaint	0	0	3	5

AE = adverse event; LCE = low-charge electrotherapy; ECT = electroconvulsive therapy.

^a Fisher's exact test, $p = 0.242$;

^b Chi-square value = 13.227, $p < 0.001$.

incidence of side effects (Ottosson, 1960a). In contrast, in our study, the LCE group experienced significantly fewer side effects than the ECT group, and severe AEs were not observed. This particular phenomenon of fewer AEs is similar to the aforementioned study; moreover, lower currents and the absence of seizures may have contributed to these results (Regenold et al., 2015). Patients with SCZ, particularly geriatric patients, who present with comorbid diseases, such as cardiovascular disease, cerebrovascular disease, diabetes, and pulmonary disorders, may exhibit an increased risk associated with ECT (Tor et al., 2017; Wilkins et al., 2008). For these special populations, LCE may reduce the risks associated with electrotherapy while maintaining the

antipsychotic effects. Due to the lower AE incidence rate, LCE has the potential to serve more patients with psychiatric disorders.

Limitations

This trial has five notable limitations. First, we assessed a small number of patients, and the number of patients who experienced AEs between the two groups was not significantly different. As this study was an exploratory pilot trial, we intend to proceed with a larger trial to assess the feasibility of LCE as a treatment for SCZ in the future. Second, a third arm using a sham ECT should be performed to further assess the potential therapeutic efficacy of LCE, but this task has proven difficult to accomplish due to the ethical concerns of exposing patients to anaesthesia when there is no expectation of a clinical benefit. Therefore, we chose routine ECT as the standard control. Third, due to the small sample and wide variety of antipsychotics, the recruited patients used various antipsychotics. However, after converting the doses to the chlorpromazine equivalent doses, the difference between the two groups was not significant. We presume that this issue would be improved in further large sample trials. Fourth, the lack of an assessment of cognitive function restricted our ability to probe the detailed conditions of patients. Thus, we will use more sensitive tests to study changes in cognitive function before and after LCE procedures. Fifth, only one male was included among the twelve patients. Although the difference in the sex ratio between the groups was nonsignificant, we should be cautious in extending our conclusions to other groups. We will collaborate with other mental health centres and hope to obtain a more balanced sex ratio in the future. Therefore, a larger study with a sufficient sample size and duration is required, along with methods for measuring biomarkers to better understand and regulate the application of ECT in the treatment of SCZ.

Preliminary conclusions

In the present pilot trial, LCE exerted an antipsychotic effect similar to ECT but was accompanied by fewer AEs. As a result, we believe that reducing the current while maintaining efficacy and no longer inducing seizures during ECT may be a feasible therapy for patients with SCZ. We are planning further studies to explore whether LCE is a potential alternative treatment for patients with SCZ.

Conflict of interest

None.

Acknowledgements

This study was supported by the Shenzhen Health and Family Planning System Research Program (Grant Number: SZFZ2017072), Science and Technology Program of Huizhou (Grant Number: 2018Y128) and CAS Pioneer Hundred Talents Program (Grant Number: 2017-074).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2018.12.143](https://doi.org/10.1016/j.psychres.2018.12.143).

References

- Alexander, L., 1950. Nonconvulsive electric stimulation therapy; its place in the treatment of affective disorders, with notes on the reciprocal relationship of anxiety and depression. *Am. J. Psychiatry* 107 (4), 241–250.
- Androp, S., 1941. Electric shock therapy in the psychoses: convulsive and subconvulsive methods. *Psychiatr. Quart.* 15 (4), 730–749.
- Bansod, A., Sonavane, S.S., Shah, N.B., De Sousa, A.A., Andrade, C., 2018. A randomized, nonblind, naturalistic comparison of efficacy and cognitive outcomes with right unilateral, bifrontal, and bitemporal electroconvulsive therapy in schizophrenia. *J. ECT* 34 (1), 26–30.
- Beran, M., Perkins, J.C., Scollon, R.W., 1952. Psychological studies on patients undergoing nonconvulsive electric-stimulation treatment. *Am. J. Psychiatry* 109 (5), 367–374.
- Dold, M., Leucht, S., 2014. Pharmacotherapy of treatment-resistant schizophrenia: a clinical perspective. *Evid. Based Ment. Health* 17 (2), 33–37.
- Fujita, Y., Takebayashi, M., Hisaoka, K., Tsuchioka, M., Morinobu, S., Yamawaki, S., 2011. Asymmetric alternation of the hemodynamic response at the prefrontal cortex in patients with schizophrenia during electroconvulsive therapy: a near-infrared spectroscopy study. *Brain Res.* 1410, 132–140.
- Grover, S., Chakrabarti, S., Hazari, N., Avasthi, A., 2017. Effectiveness of electroconvulsive therapy in patients with treatment resistant schizophrenia: A retrospective study. *Psychiatry Res.* 249, 349–353.
- Kalinowsky, L.B., Hoch, P.H., 1946. Shock treatments: and other somatic procedures in psychiatry, Shock treatments: and other somatic procedures in psychiatry.
- Kay, S.R., Fiszbein, A., Opfer, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13 (2), 261.
- Kristensen, D., Bauer, J., Hageman, I., Jorgensen, M.B., 2011. Electroconvulsive therapy for treating schizophrenia: a chart review of patients from two catchment areas. *Eur. Arch. Psychiatry Clin. Neurosci.* 261 (6), 425–432.
- Kristensen, D., Hageman, I., Bauer, J., Jorgensen, M.B., Correll, C.U., 2013. Antipsychotic polypharmacy in a treatment-refractory schizophrenia population receiving adjunctive treatment with electroconvulsive therapy. *J. ECT* 29 (4), 271–276.
- Lally, J., Tully, J., Robertson, D., Stubbs, B., Gaughran, F., MacCabe, J.H., 2016. Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: a systematic review and meta-analysis. *Schizophr. Res.* 171 (1–3), 215–224.
- Leiknes, K.A., Jarosh-von Schweder, L., Hoie, B., 2012. Contemporary use and practice of electroconvulsive therapy worldwide. *Brain Behav.* 2 (3), 283–344.
- McCall, W.V., 2010. Electroconvulsive therapy in Asia. *J. ECT* 26 (1), 1.
- Nobler, M.S., Sackeim, H.A., Solomou, M., Lubner, B., Devanand, D.P., Prudic, J., 1993. EEG manifestations during ECT: effects of electrode placement and stimulus intensity. *Biol. Psychiatry* 34 (5), 321–330.
- Olkon, D., 1957. Subconvulsive electrotherapy in mental disorders. *Dis. Nerv. Syst.* 18 (7 Part 1), 271.
- Ottosson, J.O., 1960a. Experimental studies of memory impairment after electroconvulsive therapy. The role of the electrical stimulation and of the seizure studied by variation of stimulus intensity and modification by lidocaine of seizure discharge. *Acta Psychiatr. Scand. Suppl.* 35 (145), 103–131.
- Ottosson, J.O., 1960b. Experimental studies of the mode of action of electroconvulsive therapy: Introduction. *Acta Psychiatr. Scand. Suppl.* 35 (145), 5–6.
- Petrides, G., Braga, R.J., Fink, M., Mueller, M., Knapp, R., Husain, M., Rummans, T., Bailine, S., Malur, C., O'Connor, K., Kellner, C., Group, C., 2009. Seizure threshold in a large sample: implications for stimulus dosing strategies in bilateral electroconvulsive therapy: a report from CORE. *J. ECT* 25 (4), 232–237.
- Petrides, G., Fink, M., 1996. The "half-age" stimulation strategy for ECT dosing. *Convol. Ther.* 12 (3), 138–146.
- Petrides, G., Malur, C., Braga, R.J., Bailine, S.H., Schooler, N.R., Malhotra, A.K., Kane, J.M., Sanghani, S., Goldberg, T.E., John, M., Mendelowitz, A., 2015. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am. J. Psychiatry* 172 (1), 52–58.
- Pompili, M., Lester, D., Dominici, G., Longo, L., Marconi, G., Forte, A., Serafini, G., Amore, M., Girardi, P., 2013. Indications for electroconvulsive treatment in schizophrenia: a systematic review. *Schizophr. Res.* 146 (1–3), 1–9.
- Post, R.M., Kimbrell, T.A., McCann, U., Dunn, R.T., George, M.S., Weiss, S.R., 1997. [Are convulsions necessary for the antidepressant effect of electroconvulsive therapy: outcome of repeated transcranial magnetic stimulation]. *Encephale* 23 (Spec No 3), 27–35.
- Prudic, J.M., Sackeim, H.A., Devanand, D.P., Krueger, R.B., Settembrino, J.M., 1994. Acute cognitive effects of subconvulsive electrical stimulation. *Convol. Ther.* 10 (1), 4–24.
- Regenold, W.T., Noorani, R.J., Piez, D., Patel, P., 2015. Nonconvulsive Electrotherapy for Treatment Resistant Unipolar and Bipolar Major Depressive Disorder: A Proof-of-concept Trial. *Brain Stimul* 8 (5), 855–861.
- Rosenquist, P.B., Miller, B., Pillai, A., 2014. The antipsychotic effects of ECT: a review of possible mechanisms. *J. ECT* 30 (2), 125–131.
- Sackeim, H., Decina, P., Prohovnik, I., Malitz, S., 1987. Seizure threshold in electroconvulsive therapy. Effects of sex, age, electrode placement, and number of treatments. *Arch. Gen. Psychiatry* 44 (4), 355–360.
- Sackeim, H.A., 2015. Is the seizure an unnecessary component of electroconvulsive therapy? A startling possibility. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation* 8 (5), 851–854.
- Sackeim, H.A., Prudic, J., Nobler, M.S., Fitzsimons, L., Lisanby, S.H., Payne, N., Berman, R.M., Brakemeier, E.L., Perera, T., Devanand, D.P., 2008. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation* 1 (2), 71–83.
- Small, J.G., Small, I.F., Sharpley, P., Moore, D.F., 1968. A double-blind comparative evaluation of flurothyl and ECT. *Arch. Gen. Psychiatry* 19 (1), 79–86.
- Teh, S.P., Xiao, A.J., Helmes, E., Drake, D.G., 2005. Electroconvulsive therapy practice in Western Australia. *J. ECT* 21 (3), 145–150.
- Tharyan, P., Adams, C.E., 2002. Electroconvulsive Therapy For Schizophrenia. *Cochrane Database Syst. Rev.*(2), CD000076. <https://doi.org/10.1002/14651858.CD000076>.
- Tharyan, P., Adams, C.E., 2005. Electroconvulsive Therapy For Schizophrenia. *Cochrane Database Syst. Rev.*(2), CD000076. <https://doi.org/10.1002/14651858.CD000076.pub2>.
- Tor, P.-C., Ying, J., Ho, N.F., Wang, M., Martin, D., Ang, C.P., Tan, C., Yap, L.S., Lu, V.J.M., Simpson, B., 2017. Effectiveness of electroconvulsive therapy and associated cognitive change in schizophrenia: a naturalistic, comparative study of treating schizophrenia with electroconvulsive therapy. *J. ECT* 33 (4), 272–277.
- Ulett, G.A., Smith, K., Gleser, G.C., 1956. Evaluation of convulsive and subconvulsive shock therapies utilizing a control group. *Am. J. Psychiatry* 112 (10), 795–802.
- Wilkins, K.M., Ostroff, R., Tampi, R.R., 2008. Efficacy of electroconvulsive therapy in the treatment of nondepressed psychiatric illness in elderly patients: a review of the literature. *J. Geriatr. Psychiatry Neurol.* 21 (1), 3–11.
- Zheng, W., Cao, X.L., Ungvari, G.S., Xiang, Y.Q., Guo, T., Liu, Z.R., Wang, Y.Y., Forester, B.P., Seiner, S.J., Xiang, Y.T., 2016. Electroconvulsive therapy added to non-clozapine antipsychotic medication for treatment resistant schizophrenia: meta-analysis of randomized controlled trials. *PLoS One* 11 (6), e0156510.