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ARTICLE

The maintenance of modified electroconvulsive therapy combined with risperidone is better than risperidone alone in preventing relapse of schizophrenia and improving cognitive function

Manutenção de eletroconvulsoterapia modificada combinada com risperidona é melhor do que a risperidona isoladamente na prevenção de recidivas de esquizofrenia e melhoras da função cognitiva

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ABSTRACT

Objective: To evaluate the effect of maintenance modified electroconvulsive therapy (MECT) on schizophrenic patients. **Methods:** From June 2012 to June 2014, 62 patients with schizophrenia, who had recovered from a successful course of acute MECT, were recruited. Thirty-one patients received maintenance MECT and risperidone, as the experimental group. Another 31 patients were enrolled in the control group, and received risperidone only. The effects on cognitive functions, clinical symptoms and relapse rate were determined. **Results:** Patients in the experimental group had a lower relapse rate and longer relapse-free survival time than the controls. Relative to the baseline evaluation, patients showed statistically significant improvement in verbal memory and visual memory. At the final assessment, the scores of verbal and visual memory were remarkably lower in the experimental group than the controls but there was no significant difference in other tests. **Conclusion:** Maintenance MECT plus medication is superior to medication alone in preventing relapse and improving cognitive function.

Keywords: schizophrenia; electroconvulsive therapy; risperidone; cognition.

RESUMO

Objetivo: Avaliar o efeito da manutenção de eletroconvulsoterapia modificada (ECTM) em pacientes com esquizofrenia. **Métodos:** Entre junho de 2012 a junho de 2014, 62 pacientes, com esquizofrenia e que apresentaram recuperação bem-sucedida após ECTM aguda, foram recrutados. Um grupo experimental de trinta e um pacientes recebeu ECTM de manutenção e risperidona. Os demais pacientes foram incluídos no grupo controle, recebendo apenas a risperidona. Determinou-se os efeitos sobre as funções cognitivas, os sintomas clínicos e a taxa de recidiva. **Resultados:** Os pacientes do grupo experimental tiveram menor taxa de recidiva e maior tempo de sobrevida livre de recidiva do que os do grupo controle. Em relação à avaliação inicial, os pacientes apresentaram melhora estatisticamente significativa da memória verbal e da memória visual. Na avaliação final, os escores de memória verbal e visual foram extraordinariamente menores no grupo experimental do que no grupo controle, mas não se observou diferenças significativas em outros testes. **Conclusão:** A ECTM de manutenção combinada à medicação é superior ao uso apenas de medicação na prevenção de recidivas e na melhora da função cognitiva.

Palavra-chave: esquizofrenia; eletroconvulsoterapia; risperidona; cognição.

As documented, the practice of electroconvulsive therapy (ECT) has been considered an effective management option in patients with acute schizophrenia[1]. In long-term ECT management, a distinction can be made between continuation ECT and maintenance ECT. Continuation ECT is a time-limited treatment (≤ 6 months) after an index course for relapse prevention[2]. On the other hand, maintenance ECT has no fixed end point, follows a

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successful ECT course, within the first six months at regular intervals ranging from weekly to monthly, and its objective is to prevent the recurrence of separate episodes of the illness[3]. According to the American Psychiatric Association, maintenance ECT criteria include repetitive, episodic events, which respond to ECT; being able to adapt to maintenance ECT; inability to tolerate maintenance drug treatment or ineffectiveness in preventing early exacerbations[4,5]. Nevertheless, ECT has had very little application as a form of maintenance therapy, after the acute phase of schizophrenia, although there are reports of patients who show improvement, without relapse or recurrence[6,7].

Growing evidence has demonstrated that maintenance ECT is an efficient method for therapy of drug-resistant and refractory schizophrenia[8]. Moreover, maintenance ECT has been reported to be effective for preventing recurrence of schizophrenia[9]. The National Institute for Health and Care Excellence (NICE) also reports that implementing maintenance ECT after the acute treatment has a great healing effect on relapse prevention, especially for treatment-resistant patients[10]. In addition, Lehman et al. have claimed that the combination of maintenance ECT and antipsychotics are helpful for acute schizophrenic patients who may benefit from maintenance ECT, especially intolerance sufferers and those unsuccessfully treated by maintenance antipsychotics[11]. Nevertheless, some investigators have indicated that patients have cognitive impairment after ECT and maintenance ECT[12,13]. Few studies have been performed to determine the cognitive risk of maintenance ECT, and there is no consensus on cognitive impairment due to maintenance ECT at present.

Currently, maintenance ECT is confined to case reports and retrospective studies, while there have been few randomized prospective controlled studies regarding this treatment. Herein, a prospective controlled trial of schizophrenia patients treated by maintenance modified ECT (MECT) and risperidone was implemented to determine the effect of maintenance MECT on clinical outcome and cognitive functions.

METHODS

Study design and ethics statements

This trial was a prospective randomized controlled study. The trial was approved by the Ethics Committee of Shandong Mental Health Center, and all the participants signed the informed consent prior to this study. Randomization was conducted using a random digital table by assigning the odd number to the experiment group and the even digit to the control group.

Subjects

Between June 2012 and June 2014, a total of 62 patients with an International Classification of Diseases (ICD-10) diagnosis of schizophrenia treated by MECT, who had recovered from a successful course of acute MECT were recruited from our hospital. The baseline information including demographic data, clinical diagnosis, age of onset, duration, severity of clinical symptoms and neuropsychological variables were collected. Eligible patients who met the following criteria were included:

1) age ranged from 18 to 65 years old;

2) consistent with the diagnostic criteria of ICD-10 for schizophrenia;

3) indications for acute-phase MECT: 12 patients with severe violence, six with stupor, six with suicide or self-inflicted injury, 38 with drug intolerance or poor therapeutic efficacy of medications;

4) those with Positive and Negative Syndrome Scale (PANSS) scores less than 60 points after treatment with ECT in the acute-phase, and those with stable PANSS scores after three consecutive ECT treatments.

Patients with any one of the following criteria were excluded:

1) suffering from substance abuse or dependence;

2) having received transcranial magnetic stimulation (TMS) therapy;

3) having suffered traumatic brain injury and coma;

4) severe physical disease; and

5) mental retardation.

Procedures

Patients who met the inclusion criteria were randomly assigned (1:1) to experimental and control groups. A total of 31 patients in the experimental group were treated with MECT and risperidone, and the other 31 subjects in the control received only risperidone. All MECT applications were bilateral and brief-pulsed with a constant-current device. Sessions were performed three times per week. All patients were induced with propofol (dose range of 1.5 to 2.5 mg/kg) and paralyzed with suxamethonium (1 mg/kg). The follow-ups were carried out at baseline (after the last acute-phase MECT), the second week, the fourth week and once a month afterwards, lasting for one year in total. At these follow-ups, the duration from the baseline to the relapse and the changes of cognitive function in the final evaluation were observed.

Intervention

Maintenance MECT was carried out with a Thymatron system IV ECT system (Somatic U.S.A.). Bilateral bitemporal ECT was applied, and the pulse width was set to be 0.5ms. Seizure duration was considered optimal between 25 and 60 seconds, as monitored by EEG. The initial stimulus intensity was calculated by an age-dependent method. Moreover, the seizure threshold was determined in the first MECT treatment for every subject via a standard titration protocol[14]. Generally, MECT treatment was done eight to 12 times in the acute phase, without medications. For those

treated with antipsychotics, the medications were discontinued gradually within the week prior to the acute MECT treatment. The maintenance treatment in the experimental group was carried out in the first week after acute treatment and was done once a week in the first month, once every two weeks in the second month and once a month afterwards according to a fixed schedule, lasting for one year. Thus, maintenance MECT was given in 16 sessions in total. Risperidone was increased to its therapeutic dose (≤ 8mg) within a week. If an extrapyramidal syndrome appeared, trihexyphenidyl (< 8mg) or promethazine (< 50mg) was used to manage this. Benzodiazepines and drugs for improvement of cognition function including aniracetam were forbidden. Similarly, in the control group, medication management was the same as for the experimental group. In the current study, the assessors were blind to the ECT/control group allocation, but experimenters were not blind to the MECT allocation.

Evaluation

PANSS measurement

The PANSS was used to assess the psychiatric symptoms of the patients[15]. The PANSS has 30 items (each item scores from 1 denoting "absent" to 7 denoting "severe"). The range of the total score is from 30 to 210. The instrument is clinician-rated and includes positive symptoms, negative symptoms and general pathogenic symptoms[15]. Participants are deemed to have clinical relapse if their PANSS scores are greater than 70 points twice in succession (one-week interval).

MATRICS consensus cognitive battery (MCCB)

The MCCB[16] was utilized to evaluate the cognitive function of schizophrenic patients based on the seven memory dimensions of 10 tests. The order of administration of MCCB tests was as follows:

1) processing speed, including semantic fluency, trail making test and symbolic coding;

2) attention/vigilance, which is a continuous performance test;

3) working memory, including number sequences and spatial span;

4) verbal learning and memory, including the Hopkins Verbal Learning Test-Revised;

5) visual learning and memory, including the Brief Visual Memory Test-Revised;

6) reasoning and problem-solving ability, which includes the maze test (accuracy and response time);

7) social cognition, including the emotion management test. The primitive score in each test was converted to an equivalent scale score according to norms. The higher the scores were, the better the results.

Statistical analysis

The SPSS 17.0 was employed for statistical analysis in our study. Data were expressed as mean ± standard deviation. The possibility of relapse and changes in the follow-up period were evaluated by survival analysis as well as the Kaplan-Meier method using a right-censored survival model. Moreover, the survival curves between two groups were compared by log-rank test. The clinical features, demographic variables, PANSS scores and cognitive function were compared using the student's t test and chi-square test. $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

The baseline characteristics of patients between the two groups in this study are shown in Table 1. All of the baseline data were similar between the two groups. There was no significant difference between the two groups ($p > 0.05$) in gender, age, years of schooling, age at onset, course of disease, the percentage of participants treated with no less than three types of medication prior to MECT, and PANSS score.

During the follow-up period, in the experimental group, four patients discontinued the trial because one had their telephone disconnected, one refused to be treated with MECT due to his memory deterioration, and the other two patients took sodium valproate and benzodiazepines

Table 1. Baseline characteristics of control and experimental groups.

Variables	Experimental group (n = 31)	Control group (n = 31)	p-values
Gender (male %)	54.84	61.29	0.61
Age	33.61 ± 6.86	33.00 ± 6.11	0.71
Years of schooling	9.84 ± 3.27	9.23 ± 3.06	0.45
Age of onset	25.01 ± 5.12	23.16 ± 4.30	0.15
Course of disease	9.90 ± 4.52	9.84 ± 4.37	0.96
Duration of drug use	6.48 ± 3.67	6.84 ± 3.69	0.71
The percentage of participants treated by not fewer than three types of drugs before MECT	64.52	51.61	0.30
MECT times	10.80 ± 1.93	11.48 ± 1.91	0.17
PANSS score after treatment of acute stage	53.19 ± 3.81	51.97 ± 4.18	0.23

Note: All values except for "Gender" and "The percentage of participants treated by not fewer than three types of drugs before MECT" are exhibited as mean ± standard deviation; MECT: modified electroconvulsive therapy; PANSS: positive and negative syndrome scale.

without permission. The remaining 27 participants took their medicines on schedule at the proper doses (Figure 1). In each evaluation, the information on each patient was reported by their relatives and themselves.

In the control group, five participants quit the therapy because one had a severe physical disease (renal carcinoma), one had their telephone disconnected and three participants stopped taking medication without permission. The remaining 26 participants took their medicines on schedule at the proper doses. In each evaluation, the information on each patient was reported by their relatives and themselves.

Evaluation of relapse

In the experimental group, among the 27 remaining participants, four relapsed while the remaining 23 subjects remained in stable condition till the end of the follow-up. Specifically, the four participants relapsed in the 3rd, 5th, 11th and 12th month respectively in the follow-up period. The probability of being relapse-free for six months was 0.93 ± 0.04, and the probability of being relapse-free for 12 months was 0.86 ± 0.07. Moreover, the average survival time from baseline to relapse was 11 months (95%CI: 10–12 months).

In the control group, among the 26 remaining participants, 14 relapsed while 12 remained in stable condition till the end of the follow-up. Specifically, these 14 participants relapsed in the 3rd (1 case), 4th (2 cases), 5th (2 cases), 6th (2 cases), 7th (1 case), 8th (2 cases), 10th (1 cases) and 11th (3 cases) month in the follow-up period, respectively. Seven participants relapsed in the first six months and the other seven participants relapsed in the second six months. The probability of being relapse-free for six months was 0.76 ± 0.08, and the probability of remaining relapse-free for 12 months was 0.49 ± 0.10. Additionally, the average survival time from baseline to relapse was nine months (95%CI: 8–11 months).

Compared with the control group, the patients in experimental group had a lower relapse rate and a longer relapse-free survival time ($\chi^2 = 8.7$, $p = 0.003$) (Figure 2).

Evaluation of cognitive function

At the baseline assessment, there was no significant difference in all MCCB tests between two groups ($p > 0.05$). However, relative to the baseline evaluation, all patients showed statistically significant improvement in the verbal memory and visual memory ($p < 0.05$) but no significant difference in other indexes at the final assessment in both groups ($p > 0.05$). At the final assessment, the scores of verbal and visual memory were remarkably lower in the experiment group than those in the control group ($p < 0.05$) but there was no significant difference in other tests between these two groups (Table 2).

DISCUSSION

Our trial was a prospective controlled study using standardized assessment tools. We were excited about the preliminarily proof of the effectiveness of the combination of maintenance MECT and risperidone for preventing relapse and extending the survival time in schizophrenic patients. No significant differences were observed between the experimental and control groups in most of cognitive tests, except verbal and visual memory.

Previous case reports and small-scale open trials have demonstrated that maintenance ECT is effective in drug-resistant schizophrenia[17,18]. Chanpattana and coworkers have indicated that compared with maintenance ECT alone or flupentixol alone, the combination of maintenance ECT and flupentixol is more effective in preventing the relapse of schizophrenia[19]. Moreover, a former case report

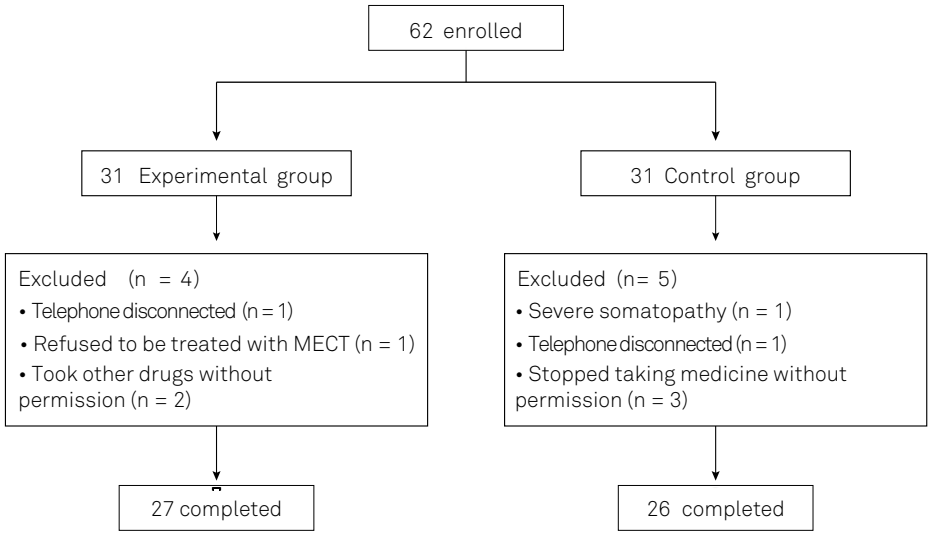

Figure 1. Flow of patients with schizophrenia through a randomized, prospective controlled trial evaluating the efficacy of maintenance modified electroconvulsive therapy (MECT).

provided by Kitamura et al.[20] demonstrated that a 71-year-old female patient with schizophrenia achieved a complete remission when she was maintained for six years on maintenance ECT without antipsychotic medication. A retrospective review of 19 refractory schizophrenic and schizoaffective patients with maintenance ECT indicated that maintenance ECT plus medication might be an effective alternative, relative to pharmacotherapy alone[9]. Our results were consistent with the results mentioned above. Based on our results, the combination of maintenance MECT and risperidone for preventing relapse in schizophrenia patients is superior to risperidone alone.

Memory impairment has always been regarded as the most troublesome and prominent side effect of ECT over a short period[21]. However, there is still no definitive conclusion to the question of whether maintenance ECT is responsible for cognitive impairment. Several studies have suggested that cognitive function remains stable during maintenance ECT, and cognitive function during the maintenance stage of treatment does not differ between ECT and pharmacotherapy groups[22,23,24]. In the current study, relative to the baseline evaluation, patients showed statistically significant improvement in verbal memory and visual memory at the final evaluation. This indicates that maintenance MECT may improve cognitive function of schizophrenic patients to some degree. However, at the final assessment, verbal and visual memory was remarkably lower in the experiment group than those in the control group. Thus, our preliminary results need to be validated, with more samples and a more rigorous design.

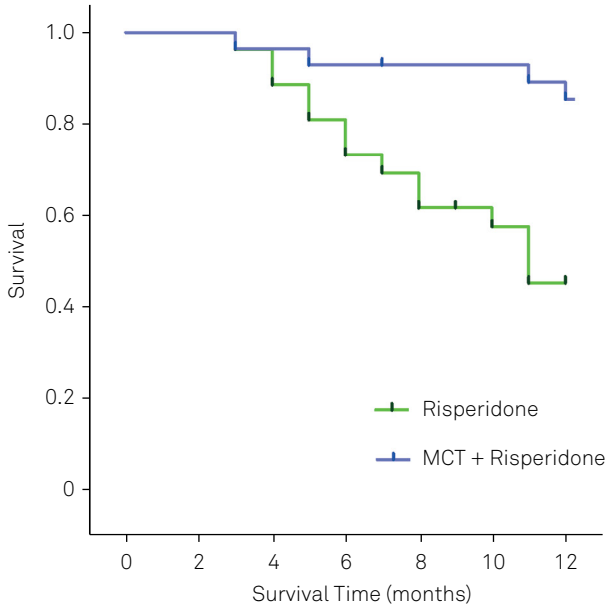

Figure 2. Survival curves of experimental and control groups.

Some refractory patients were involved in this study. Generally, such patients should be treated with clozapine, which is the best evidence-based option for treatment-resistance schizophrenia[25]. However, a large proportion of clozapine-treated patients exhibit a partial response to therapy, while risperidone is relatively safer when compared with clozapine. Besides, after treatment with acute-phase MECT, some participants might be more sensitive to risperidone. Considering the above facts, the current trial selected risperidone as the control.

To the best of our knowledge, our study was the first prospective randomized controlled trial with masked evaluators rating the efficacy of maintenance MECT plus risperidone for patients with schizophrenia. Moreover, based on the preliminary results, maintenance ECT combined with medication might be an effective alternative to pharmacological treatment alone in schizophrenia, which is in line with a previous controlled study by Chanpattana et al.[19], who indicated that the combination of maintenance ECT and flupenthixol was superior to flupenthixol or maintenance ECT alone. This alternative therapy is crucial in this field, because of the important public health problems raised. Further research is definitely required in an attempt to create and standardize guidelines for prescription, and maintenance ECT for schizophrenic patients.

The limitations of this study should be considered. To begin with, there was a relatively small sample size, which may have weakened the statistical power. Furthermore, the frequency of maintenance MECT was fixed, without individualized

Table 2. Comparison of cognitive function of control and experimental groups.

Variables	Baseline evaluation		Final evaluation	
	Experimental group	Control group	Experimental group	Control group
Trail making test	41.45 ± 3.47	40.94 ± 2.54	41.16 ± 4.05	39.61 ± 4.29
Symbolic coding	40.65 ± 5.64	41.97 ± 6.48	41.19 ± 6.04	42.03 ± 6.72
Verbal memory	36.32 ± 3.64	37.81 ± 3.95	44.58 ± 3.01$^{\#}$	46.84 ± 5.35$^{*\&}$
Spatial span	40.00 ± 3.73	40.68 ± 4.76	40.61 ± 4.13	41.81 ± 4.32
Number sequences	40.71 ± 3.57	41.48 ± 3.52	41.61 ± 3.27	40.87 ± 3.00
Maze test	38.42 ± 3.85	39.61 ± 4.38	39.90 ± 2.84	40.74 ± 3.92
Visual memory	40.97 ± 4.38	39.45 ± 4.09	43.06 ± 4.82$^{\#}$	46.23 ± 3.86$^{*\&}$
Semantic fluency	43.00 ± 4.18	42.03 ± 4.75	42.29 ± 3.55	42.71 ± 4.94
Emotion management	43.61 ± 5.75	42.61 ± 5.21	44.10 ± 5.85	43.16 ± 7.25
Continuous performance test	43.16 ± 6.14	41.87 ± 5.50	43.42 ± 6.05	40.90 ± 5.92

Note: All values are exhibited as mean ± standard deviation; $^{\#}p < 0.05$ vs. experimental group at baseline evaluation; $^{*}p < 0.05$ vs. control group at baseline evaluation; $^{\&}p < 0.05$ vs. experimental group at final evaluation.

assessments, which increased the risk of relapse and additional side effects for those schizophrenics who did not need this frequency.

Taken together, the combination of maintenance MECT and risperidone is superior to risperidone alone in preventing relapse in schizophrenic patients. Moreover, maintenance MECT plus risperidone may improve cognitive function to an extent. However, our preliminary results need to be validated, based on more samples and a more rigorous design.

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