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ORIGINAL ARTICLE

The Effectiveness of Non-clozapine Antipsychotics Combined with Electroconvulsive Therapy versus Clozapine Combined with Electroconvulsive Therapy for Treatment-resistant Schizophrenia

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ABSTRAK

Objektif kajian ini ialah untuk membandingkan keberkesanan dan keselamatan ubat antipsikotik atipikal lain jenis bukan clozapine yang dikombinasikan dengan terapi elektrokonvulsif (ECT) (NC+ECT) melawan clozapine bersama rawatan ECT (C+ECT) untuk merawat skizofrenia yang resistan terhadap rawatan (TRS). Kami mengkaji data 32 pesakit yang mengalami TRS yang menerima ECT. Kami membandingkan ciri klinikal, tindak balas terhadap rawatan [ditakrifkan sebagai peningkatan 40% dalam skala kecil gejala psikotik mengikut Skala Penarafan (BPRS) dari skor pra-rawatan], perubahan skor ujian status mini mental (MMSE), dan kesan buruk yang lain antara kumpulan NC+ECT (N = 16) dan kumpulan C+ECT (N = 16). Hasil kajian menunjukkan kadar respons keseluruhan adalah 65.6% (75.8% untuk kumpulan NC+ECT dan 56.3% untuk kumpulan C+ECT, p = 0.26). Skor BPRS keseluruhan di kedua-dua kumpulan menurun dengan ketara, perbezaan min dalam jumlah skor subskala psikotik BPRS antara pra-ECT dan selepas ECT terakhir adalah 10.4 ± 5.8 (p<0.001) untuk kumpulan NC+ECT dan 6.6 ± 7.3 (p = 0.002) untuk kumpulan C+ECT masing-masing. Semasa membandingkan kumpulan NC+ECT dengan kumpulan C+ECT, perbezaan min dalam jumlah skor subskala psikotik BPRS didapati tidak signifikan (p = 0.104). Perbezaan min skor MMSE antara pra-ECT dan selepas ECT terakhir adalah -1.1 ± 5.1 (p = 0.45) untuk kumpulan NC+ECT dan 0.2 ± 4.3 (p = 0.855) untuk kumpulan C+ECT. Perubahan skor MMSE dalam kumpulan NC+ECT tidak berbeza berbeza dengan kumpulan C+ECT (p = 0.461). Kesimpulannya, gabungan antipsikotik dan ECT adalah pilihan rawatan yang berkesan dan selamat bagi pesakit dengan TRS. Keberkesanan antipsikotik atipikal lain serta keberkesanan kumpulan ECT mungkin setanding

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dengan clozapine bersama-sama rawatan ECT.

Kata kunci: farmakoterapi, gangguan psikotik, kecacatan kognitif, rangsangan otak

ABSTRACT

The study aimed to compare the effectiveness and safety of other atypical antipsychotics (non-clozapine) plus electroconvulsive therapy (ECT) (NC+ECT) versus clozapine plus ECT (C+ECT) for treating treatment-resistant schizophrenia (TRS). Data of 32 patients with TRS who was receiving ECT were analysed. We compared clinical characteristics, response to treatment [defined as an improvement of 40% in the Brief Psychotic Rating Scale (BPRS) psychotic symptom subscale from pretreatment scores], change of Mini-mental Status Exam (MMSE) scores, and other adverse effects between the NC+ECT group (N= 16) and C+ECT group (N =16). We found that the overall response rate was 65.6% (75.8% for the NC+ECT group and 56.3% for the C+ECT group, p=0.26). The overall BPRS score in both groups decreased significantly. The mean difference in total BPRS psychotic subscale score between pre-ECT and after last ECT was 10.4 $\pm$ 5.8 ($p<0.001$) for the NC+ECT group and 6.6 $\pm$ 7.3 ($p = 0.002$) for the C+ECT group. When comparing the NC+ECT group to the C+ECT group, the mean difference in total BPRS psychotic subscale score was not significant. ($p = 0.104$). The mean difference in MMSE score between pre-ECT and after the last ECT was -1.1 $\pm$ 5.1 ($p =0.45$) for the NC+ECT group and 0.2 $\pm$ 4.3 ($p=0.855$) for the C+ECT group. The change of MMSE score in the NC+ECT group was not significant different compare to the C+ECT group ($p = 0.461$). We concluded the combination of antipsychotics and ECT is an effective and safe treatment option for patients with TRS. Other NC+ECT groups' efficacy may be comparable to that of clozapine plus ECT.

Keywords: brain stimulation, cognitive impairment, pharmacotherapy, psychotic disorders

INTRODUCTION

Schizophrenia is a chronic and debilitating disease that affects a person's quality of life and their jobs, marriage and parenting prospects. Approximately 30% of patients responded poorly to antipsychotics treatment (Brenner et al. 1990). Patients with refractory symptoms usually have severe functional impairments. Treatment-resistant schizophrenia (TRS) is defined as the continuations of symptoms after two trials of appropriate doses and duration of antipsychotic medications (Potkin et al. 2020).

Clozapine is a second-generation antipsychotic that is the most effective medication for TRS but may

produce fatal adverse reactions (Haas et al. 2007; Ittasakul et al. 2016). Recommended clozapine dosage is 300-600 mg/day for Caucasians and 150-300 mg/day for Asians to reach the therapeutic level of 350 ng/ml (de Leon et al. 2020). Common side effects of clozapine include hypersalivation, excessive sedation, weight gain, metabolic abnormalities, tachycardia, dizziness, and constipation. Clozapine comes with "black box" warnings about the risk of agranulocytosis, seizures, myocarditis, orthostatic hypotension, and increased mortality in older patients with dementia-related psychosis. However, 40-70% of patients with TRS do not respond to clozapine (Siskind et al. 2017).

Studies suggest that electroconvulsive therapy (ECT) is a safe treatment modality and can effectively treat schizophrenia. To reduce psychotic symptoms, a combination of ECT and antipsychotics is often used to treat TRS. Previous studies demonstrated a combination of ECT and clozapine was more effective than using clozapine alone to reduce psychotic symptoms (Kim et al. 2018; Petrides et al. 2015; Wang et al. 2018). Patients who received ECT and clozapine had an increased frequency of self-reported memory impairment and headache compared to those treated with clozapine alone (Wang et al., 2018). However, the combination of ECT and other antipsychotics (for example, olanzapine, ziprasidone, quetiapine) can also be an effective and well-tolerated treatment option for schizophrenia (Zheng et al. 2016). Research on the effectiveness and safety of combining ECT and antipsychotics is limited.

In Thailand, ECT is commonly combined with antipsychotics to treat TRS (Chanpattana & Kramer 2004; Pitidhrammabhorn et al. 2016). Thus, this research aimed to compare the effectiveness and safety of other atypical antipsychotics (non-clozapine) plus electroconvulsive therapy (NC+ECT) to clozapine plus ECT (C+ECT) for treating patients suffering from TRS. This study will help clinicians decide if they should wait until clozapine fails before adding ECT or whether it can be used for treatment augmentation before starting clozapine for patients with TRS.

MATERIALS AND METHODS

Setting and Study Design

The Human Research Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University approved the study protocol (COA.MURA2020/576). Patients gave their written informed consent. The research was undertaken in accordance with the Declaration of Helsinki of the World Medical Association (World Medical Association 2013).

We performed a retrospective study to compare the effectiveness and safety of other NC+ECT and C+ECT for treating patients with TRS at the Ramathibodi Hospital, Bangok, Thailand. We conducted chart reviews for all patients with TRS who received inpatient ECT from January 2013 to December 2020. Psychiatrists performed diagnosis based on the

Table 1: Dose titration schedule and parameter settings for ECT devices

Step	Thymatron System IV				Mecta Spectrum 5000Q				
	Pulse width (ms)	Frequency (Hz)	Energy level (%)	Charge (mC)	Pulse width (ms)	Frequency (Hz)	Duration (Sec)	Current (mA)	Charge (mC)
1	0.5	40	10	50	1	40	0.75	800	48
2	0.5	40	15	76	1	40	1.25	800	80
3	0.5	40	25	126	1	40	2.0	800	128
4	0.5	40	35	176	1	60	2.0	800	192
5	0.5	40	50	252	1	60	3.0	800	288
6	0.5	60	70	353	1	60	4.5	800	432
7	1.0	40	100	504	1	60	6.0	800	576

DSM-V criteria (American Psychiatric Association 2013). The TRS is defined as the continuations of symptoms after more than two trials of appropriate dose and duration (at least 4-6 weeks) of antipsychotic medications (Potkin et al. 2020).

We collected demographic data, as well as information regarding clinical characteristics including age, gender, age of onset, duration of illness, number of failed antipsychotics prior, ECT data (e.g. indications, stimulus dose, electrode placement method, and number of sessions), antipsychotic treatments (type and a dose of antipsychotic), and clinical variables pre- and post-ECT: the Brief Psychiatric Rating Scale (BPRS) (Leucht et al. 2005; Thompson et al. 1994) and the Mini-Mental State Examination (MMSE) (Folstein et al. 1975).

ECT Procedure

Before receiving ECT, all patients were evaluated by psychiatrists and anesthesiologists. At least 15 hours before ECT treatment, benzodiazepines were stopped. ECT procedures were carried out by psychiatrists, psychiatric residents, anesthetic nurses, psychiatric nurses, and anesthesiologists in the post-anesthetic care unit (PACU). Anesthesia with thiopental (2-5 mg/kg IV) or propofol (1-2 mg/kg IV) and succinylcholine (0.5-1 mg/kg IV) was administered. ECT was administered three times/week using the brief pulse wave generated by a Mecta Spectrum 5000Q (Mecta Corp, USA) or Thymatron System IV (Somatics, Northampton, USA). All patients with schizophrenia in our clinic had ECT with bilateral (BL) electrode placement and a pulse width of 1.0 milliseconds.

The seizure threshold (ST) was determined at the first ECT session by using the dose-titration method. Dose titration schedule was described in the Table 1. The ST was defined as the dose at which there was definite evidence on the electroencephalogram of generalised seizure activity for at least 25 seconds. The stimulus intensity was then increased to 50% above the ST for BL electrode placement (Ittasakul et al. 2019).

The BPRS (Leucht et al. 2005; Thompson et al. 1994) and MMSE

(Folstein et al. 1975) were used to assess the severity of psychotic symptoms and cognition of the patients at baseline (24 hours before ECT), and after the last ECT session. The BPRS is an 18-item rating scale that is commonly used to assess the severity of symptoms in schizophrenia patients. Each item is graded on a scale of one to seven, with one being the absence of a symptom and seven being the presence of a symptom (extremely severe) (Thompson et al. 1994). MMSE is a 30-point questionnaire widely used to measure cognitive functions, including orientation, memory, attention, concentration, recall, language, ability to follow commands, and visuospatial function (Folstein et al. 1975).

Staff and psychiatric residents who had obtained proper training conducted the assessments. The Intraclass Correlation Coefficient (ICC) was used to evaluate inter-rater reliability. The ICC was 0.9 for BPRS and MMSE. Treatment was typically stopped when maximal improvement (remission or plateau of effect) was reached as assessed by BPRS scales or when adverse effects limited further treatments. Remission was defined as BPRS < 31 for schizophrenia (Leucht et al. 2005).

Outcome Measures

The primary outcome was response to treatment, which defined as an improvement of 40% (Andreasen et al. 2005; Petrides et al. 2015) in the BPRS psychotic symptom subscale (hallucinatory behavior, suspiciousness, conceptual disorganisation, and unusual thought content) from pretreatment scores and last ECT treatment score. Secondary outcomes were a change of MMSE scores, adverse effects during ECT treatment. We also assessed the other adverse effects, including post-ECT delirium, headache, myalgia, nausea/vomiting and dizziness.

Statistical Analysis

We analysed and compared the clinical characteristics of the patients, clinical outcomes (response rate, change of total BPRS, BPRS psychotic symptoms subscale, MMSE scores), adverse effects between the NC+ECT group and C+ECT group. For continuous and categorical outcomes, data were given as mean with standard deviation (SD) and percentages, respectively.

We examined the data distribution to determine which statistical test to use. Non-normally distributed parameters were compared using corresponding non-parametric tests (Wilcoxon sign rank and Mann-Whitney U tests). Continuous measurements were compared using dependent or independent t-tests, as indicated. The chi-squared and Fisher's exact tests were used to compare categorical parameters, as indicated. We used a two-way repeated measure analysis of variance (ANOVA). The two groups (NC+ECT group and C+ECT group) as a between subjects' factor and the two measurements (pre-ECT and post ECT) during treatment as the within-subjects factor (time) were considered. Test of sphericity was based on results of a Greenhouse–Geisser correction.

In both groups, missing data was imputed using the last-observation-carried-forward (LOCF) method. SPSS 21.0 for Windows was used for all statistical analysis (IBM Corp., Armonk, NY, USA). The p-value for statistical significance was determined to be less than 0.05.

RESULTS

Sample Description

Thirty-two patients with TRS received inpatient ECT from January 2013 to December 2020. The clinical characteristics of the 32 patients are shown in Table 2. For the severity of symptoms, the total BPRS score before ECT was 53 ± 17.7 (range 26-103).

Among all 32 patients, 16 (50%) patients were in C+ECT group, a dosage of clozapine was 180.5 ± 90.5 mg/day and 16 (50 %) patients were in the NC+ECT group. Among these 16 patients, 8 (50%) received quetiapine (281.3 ± 234.8 mg/day), 7 (38.9%) received risperidone (4.3 ± 2.1 mg/day), 4 (25%) received olanzapine (16 ± 8.5 mg/day), 2 (11.1%) received paliperidone oral form (10.5 ± 2.1 mg/day) and 2 (11.1%) received aripiprazole (30 mg/day).

Patients who received C+ECT compared to NC+ECT had an earlier age of onset (23.6 7.8 years versus 31.6 ± 11.2 years, t = 2.2, df = 27, p = 0.033), but were statistically similar for all other parameters.

Response Rate and Change of Psychiatric Symptoms

Of 32 patients, 21 (65.6%) were responders with >40% reduction of BPRS psychotics symptom subscale after the last ECT sessions. The response rate was 75.8% (12/16) for the NC+ECT group and 56.3% (9/16) for the C+ECT group, respectively. No statistically significant difference in response rate between NC+ECT

Table 2: Demographic data and clinical characteristics (N=32)

Clinical characteristics	Mean ± SD or n (%)			p-value
	All patients (n =32)	Non-clozapine antipsychotic plus ECT (n=16)	Clozapine plus ECT (n =16)	
Age (years)	44.1 ± 14.9	45.6 ± 16.3	41.1 ± 13.2	0.418
Age of onset (years)*	27.7 ± 10.4	31.6 ± 11.2	23.6 ± 7.8	0.033
Duration of illness (year)	15.3 ± 7.4	14.4 ± 6.9	16.3 ± 8.1	0.523
Number of ECT sessions	12.8 ± 6.4	13.3 ± 6.0	12.8 ± 7.0	0.812
Seizure threshold	126.6 ± 69.5	136.6 ± 64.3	125.4 ± 75.0	0.654
Gender Male Female	 17 (53.1%) 15 (46.9%)	 9 (56.3%) 7 (43.8%)	 8 (50%) 8 (50%)	0.723
Number of concurrent psychotropic medications	2.5 ± 1.5	2.1 ± 1.2	3 ± 1.8	0.082

*p<0.05, ECT = electroconvulsive therapy, SD = standard deviation

and C+ECT group after last ECT was observed (Chi-square 1.25, df =1, P value = 0.26).

Total BPRS Score

The total BPRS score at baseline was 55.2 ± 22.2 for the NC+ECT group and 50.8 ± 13.4 for the C+ECT group. There was no significant difference between groups at baseline (t = 0.78, df = 30 p = 0.442). After the last ECT, the total BPRS score was 28.3 ± 13.9 for the NC+ECT group and 27.8 ± 12.3 for the C+ECT group, and there was no significant difference between groups after the last ECT (t = 0.94, df = 30 p = 0.926).

The overall BPRS score in both groups decreased significantly. The mean difference in total BPRS score between pre-ECT and after the last ECT was 27.6 ± 19.2 (t = 5.73, df =15, p<0.001) for the NC+ECT group and 22.9 15.4 (t = 5.95, df = 15, p<0.001) for the C+ECT group. When comparing the NC+ECT group to the C+ECT group, the mean difference in total BPRS score was not statistically significant (t = 0.75, df = 30, p = 0.459). A two-way ANOVA showed the main effect of time on total BPRS score was statistically significant [F (1, 30) = 67.1, p<0.001]. The main effect of treatment group on the total BPRS score across time was not statistically significant [F (1,30) = 0.388, p=0.565)]. There was no significant effect of an interaction between time and group [F (1, 30) = 0.563, p = 0.459].

Total BPRS Psychotic Symptoms Subscale Score

The total BPRS psychotic subscale score at baseline was 18.6 ± 5.9 for the NC+ECT group and 15.9 ± 4.3 for the C+ECT group, and there was no significant difference between groups at baseline (t = 1.5, df = 30 p = 0.141). The total BPRS psychotic subscale score after the last ECT was 8.3 ± 5.1 for the NC+ECT group and 9.3 ± 6.4 for the C+ECT group, and there was no significant difference between groups after the last ECT (t = -0.5, df = 30 p = 0.627).

The overall BPRS psychotic subscale score in both groups decreased significantly. The mean difference in total BPRS psychotic subscale score between pre-ECT and after the last ECT was 10.4 ± 5.8 (t = 8, df =15, p<0.001) for the NC+ECT group and 6.6 ± 7.3 (t = 3.6, df = 15, p = 0.002) for the C+ECT group. When comparing the NC+ECT group to the C+ECT group, the mean difference in total BPRS psychotic subscale score was not statistically significant (t = 1.7, df = 30, p = 0.104).

A two-way ANOVA showed the main effect of time on total BPRS psychotic subscale score was statistically significant [F (1, 30) = 57.8, p<0.001]. The main effect of the treatment group on the total BPRS psychotic subscale score across time was not statistically significant [F (1,30) = 0.308, p = 0.583]. There was no significant effect of an interaction between time and group [F (1, 30) = 2.814, p = 0.104].

Safety and Tolerability

Regarding MMSE score, 4 patients (two patients in the NC+ECT group and two in the C+ECT group) were excluded

from data analysis because data were missing.

The MMSE score at baseline was 23.1 ± 5.1 for the NC+ECT group and 24.8 ± 3.8 for the C+ECT group, with no significant difference between groups at baseline (t = -0.96, df = 26 p = 0.347). The MMSE score after the last ECT was 24.2 ± 4.3 for the NC+ECT group and 24.6 ± 3.8 for the C+ECT group, with no significant difference between groups after the last ECT (t = -0.2, df = 26 p = 0.818).

The MMSE score in both groups did not change significantly after the last ECT. The mean difference in MMSE score between pre-ECT and after the last ECT was -1.1 ± 5.1 (t = -0.8, df = 13, p = 0.45) for the NC+ECT group and 0.2 ± 4.3 (t = 1.9, df = 13, p = 0.855) for the C+ECT group. When comparing the NC+ECT group to the C+ECT group, the mean difference in MMSE score was not statistically significant (Mann-Whitney U = 82, Z =-0.7 p = 0.461).

A two-way ANOVA showed the main effect of time on MMSE score was not statistically significant [F (1, 26) = 0.228, p = 0.637]. The main effect of treatment group on the MMSE score across time was not statistically significant [F (1,26) = 0.542, p= 0.468]. There was no significant effect of an interaction between time and group [F (1, 26) = 5.786, p = 0.514]. Furthermore, no significant difference of other side effects during ECT and post ECT between NC+ECT and C+ECT groups was observed (Table 3).

DISCUSSION

According to our findings, the combination of antipsychotics and ECT may be beneficial for patients with schizophrenia. The response rate at the endpoint was 65.6% (75.8% for the NC+ECT group and 56.3% for the C+ECT group). This result was in line with previous studies, which found that patients with treatment-resistant schizophrenia responded to the combination of antipsychotics and ECT at 50-55% (Chan et al. 2019; Chanpattana & Kramer 2003; Petrides et al. 2015). In addition, there were significant improvements in BPRS and BPRS psychotic symptoms subscale scores in both NC+ECT and C+ECT group after the last ECT which was consistent with previous studies that demonstrated combination therapy of antipsychotics and ECT improved

Table 3: Other adverse effects

	Non-clozapine antipsychotic plus ECT (n =16)	Clozapine plus ECT (n =16)	Chi-square	df	p-value
Post-ECT delirium	-	1 (6.3%)	1	1	1.000
Headache	9 (56.3%)	11 (68.8%)	0.5	1	0.465
Myalgia	5 (31.3%)	2 (12.5%)	1.6	1	0.394
Nausea/vomiting	3 (18.8%)	3 (18.8%)	< 0.001	1	1.000
Dizziness	3 (18.8%)	5 (31.3%)	0.7	1	0.685

ECT = electroconvulsive therapy

psychotic symptoms in patients with schizophrenia (Ahmed et al. 2017; Chan et al. 2019; Chanpattana & Chakrabhand 2001; Kim et al. 2018; Lally et al. 2016).

When the NC+ECT group and the C+ECT were compared, there was no difference in response rate, total BPRS score change, and BPRS psychotic symptoms subscale score after the last ECT. This finding contradicts a previous study by Ahmed et al. (2017) that found C+ECT was superior to other antipsychotics plus ECT. This may be explained by variations in clozapine dosage and type of antipsychotics in the non-clozapine antipsychotic group. Compared to the previous report, the dosage of clozapine was lower (180.5 mg/day versus 525 mg/day) in the present study. However, recommended clozapine dosage is 300-600 mg/day for Caucasians and 150-300 mg/day for Asians to reach the therapeutic level of 350 ng/ml (de Leon et al. 2020). Furthermore, flupentixol and chlorpromazine were the most common antipsychotics in previous studies, while atypical antipsychotics were the focus in the present study.

In terms of safety and tolerability, we observed no substantial difference in MMSE score between baseline and post-ECT in both the C+ECT group and non-NC+ECT group. This finding was similar to that of a previous study by Petrides et al. (2015). Regardless, some studies have shown that a combination of ECT and antipsychotics may result in minimal cognitive side effects and in some cases, improved cognition (Chan et al. 2019; Kaster et al. 2017; Tor et al. 2017; Vuksan Ćusa et al. 2018). The disparity in cognitive outcomes may be explained by the possible difference in the method of ECT administration in those studies. Other adverse effects, such as post-ECT delirium, headache, myalgia, nausea/vomiting, and dizziness, were not significantly different between NC+ECT and C+ECT groups.

One of the study's strengths was that it explored the effectiveness of C+ECT as compared to the other NC+ECT in patients with schizophrenia. This study, however, has a number of limitations. As the participants were all inpatients at a Thai university hospital, the findings should be interpreted with caution in other settings. Secondly, the sample size was tiny, perhaps resulting in a type II error. Thirdly, clozapine level was not measured in this analysis. Fourthly, we did not analyse psychiatric comorbidities that emerged with schizophrenia. Finally, the data was just for acute ECT; additional research into long-term follow-up after therapy is needed.

CONCLUSION

The combination of antipsychotics and ECT is an effective and safe treatment option for patients with TRS. Other NC+ECT groups' efficacy may be comparable to that of C+ECT. Further randomised control trials are needed to investigate the efficacy and side effects differences between the two groups.

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