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COMPARATIVE STUDY OF CLOZAPINE, ELECTROSHOCK (ECT), AND THE COMBINATION OF ECT WITH CLOZAPINE IN TREATMENT-RESISTANT SCHIZOPHRENIC PATIENTS

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ABSTRACT

Eighteen treatment-resistant schizophrenic patients were assigned to three equal groups: one group was given clozapine; one group was treated with ECT; and one group was treated with the combination of clozapine and ECT. The treatment response was evaluated using the PANSS criteria, and the data were analyzed with ANOVA. Combination therapy was superior to single modality therapy. The reduction of PANSS scores was 46% in the clozapine group, 40% in the ECT groups, and 71% in the combination group; the difference between the combination group and the other groups was statistically significant ($P<0.05$). Patients had a quick response to combination treatment, which resulted in a higher cure rate of positive and negative symptoms and improved the patients' general performance. There were no significant adverse effects with combination treatment. Combination treatment with clozapine and ECT was safe and effective in treatment-resistant schizophrenic patients. It should be considered for the treatment of treatment-resistant schizophrenic patients.

Key words: Treatment-resistant schizophrenic patient, clozapine, ECT, combination of ECT and clozapine.

INTRODUCTION

With the discovery of antipsychotic drugs in the last 5 decades, particularly the new generation of drugs in the past few years, many schizophrenic patients respond well to treatment and can return to their normal lives. However, about 25-30% of schizophrenic patients do not respond to such drug treatment and are considered to be resistant (Kaplan and Sadock, 2003). Resistant patients are defined as those who do not respond to two separate groups of antipsychotic drugs (at a dose equivalent to 20 mg/l of haloperidol per day) after 6 weeks of treatment (Kaplan and Sadock, 2003). In the past few years, clozapine and, in some cases, ECT was given to such patients, though their effect was not satisfactory. In contrast to the typical antipsychotic medications that are primarily antagonists of D2 dopamine receptors, clozapine has little effect on this receptor; clozapine acts more through the D_1, $D_{3,}$ and D_4 dopamine and serotonin 5 H T_{2A} receptors (Kaplan and Sadock, 2003). Though the precise mechanism of ECT is not clear, it is thought that the decline in brain metabolism that occurs after the convulsion has therapeutic properties. Furthermore, ECT has different effects on various neurotransmitters that are not yet understood. Clozapine and ECT have different mechanisms and have both been used in resistant cases, but the results have not been satisfactory. In recent years, different approaches have been suggested to treat resistant schizophrenia, including rispervidin, clozapine (Chouinard *et al.*, 1994), olanzapine (Conley *et al.*, 1998, Launer, 1997, Ratakonda *et al.*, 1997, Sheitman *et al.*, 1997), supplemental glycine (Potkin *et al.*, 1999), famotidine (Oyewumi *et al.*, 1994), and low dose bromocryptine (Wolf *et al.*, 1992); however, none of them have produced satisfactory results. Recently, the combination of clozapine and ECT has been found promising in preliminary studies. In 1999, Kales *et al.* reported the efficacy of this method in treating 5 schizophrenic patients (Kales and Dequardo, 1999). In 2000, Kupchik and Spiva studied 36 schizophrenic patients who were resistant to the classic antipsychotics, clozapine, and ECT, and found that the combination of clozapine and ECT was useful in 67% of patients. In 2004, Kho and Blansjaar successfully treated 8 of 11 schizophrenic patients who were resistant to clozapine and other antipsychotics with a combination of clozapine and ECT. Various case reports have reported the efficacy of clozapine and ECT used in combination. In fact, most of the data on the use of the combination of clozapine and ECT have been from case reports; no comparison studies have been done in which the effects of combination therapy were compared with the effects of either treatment alone. Thus, the aim of this study was to determine the safety and effectiveness of combination therapy in treatment-resistant patients, and whether combination therapy is better than previous therapies.

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MATERIALS AND METHODS

In this clinical trial, 18 treatment-resistant schizophrenic patients were selected from among the patients admitted to Zareh hospital. The diagnosis of schizophrenia was based on the DSM-IV criteria and was confirmed by two psychiatrists (the consulting physician and the researcher). Resistance was defined as lack of response to two separate groups of antipsychotics given at the proper dose for a sufficient time. Patients with a history of seizures, clozapine-induced seizures, previous adverse effects on the bone marrow with clozapine, and WBC count below 3500 were excluded from the study. At the beginning of treatment, a chest X-ray, WBC, and EKG were obtained, and an anesthesia consultation was performed. During treatment, weekly CBCs were obtained; cases in which the WBC count fell below 3500 or was reduced by more than 30% of the previous count were excluded from the study and referred to a hematologist. All patients gave their written informed consent prior to beginning treatment. The patients were matched according to age, gender, type of schizophrenia, and symptom severity (based on the PANSS criteria). The patients were divided into 3 equal groups of 6 subjects (3 men and 3 women) each. In each group, there were 3 paranoid schizophrenias, two disorganized, and one undifferentiated. One group was treated with clozapine (after first determining the appropriate dose for 8 weeks); one group was treated with ECT (12 sessions using the standard unilateral method); and one group was treated with a combination of ECT and clozapine. In the group that received clozapine alone, patients were given placebo ECT, consisting of drug-induced sedation without seizure induction in the ECT room. The group that received ECT alone was given a clozapine placebo. Prior to treatment, the patients were drug-free for a 2-week wash-out period. The PANSS test was used to evaluate the patients' symptom severity at the beginning of treatment and then biweekly to evaluate their response to treatment. Each patient had 5 PANSS tests administered by a postgraduate psychiatry resident in a double-blind manner. The MMSE test was also used to assess possible cognitive side effects. The base dose of clozapine was 200 mg; based on the patient's response, the dose was increased as needed. The minimal number of ECT sessions was 12 (3 times weekly for 4 weeks). The data were analyzed using SPSS with multi-step measurement or repeated ANOVA..

RESULTS

Each group consisted of 3 men and 3 women. The mean age was 31 years in the clozapine group, 33 years in the ECT group, and 31 years in the combined therapy group (Table 1).

Table 1. Patients' demographic features by group

Group Variable		Clozapine	ECT	Combined therapy
Mean age (years)		31	33	30
Gender	Male	3	3	3
	Female	3	3	3

The three groups were matched for age and gender ($p< 0.05$).

The total mean PANSS score at the beginning of treatment was 96 in the clozapine group, 99 in the ECT group, and 99 in the combined therapy group; these scores were not significantly different.

The mean positive and negative symptom scores were 23 and 32, respectively for the clozapine group, 31 and 25, respectively, for the ECT group, and 33 and 26, respectively, for the combined therapy group; there were no significant differences among the groups. A reduction in the PANSS score reflects response to treatment; a greater reduction in the PANSS score implies a better response to treatment. In the clozapine group, there was 46% reduction in the mean PANSS score with treatment (before, 96 and after, 52; $F=239.91$, $df =4; 20$, $P< 0.0001$). In the ECT group, there was 40% reduction in the mean PANSS score (before, 99 and after, 60; $F = 446.8$, $df =4; 20$, $P < 0.0001$) . In the combined therapy group, there was 71% reduction in the mean PANSS score (before, 99 and after, 29; $F=1110.1$, $df =4; 20$, $P< 0.00001$). The analysis showed that, while all 3 groups had a statistically significant response to treatment, the combination therapy group had a statistically significantly greater response than the other 2 groups ($F=189.15$, $df =4, 63$, $P < 0.0001$) (Table 2).

Furthermore, the combination therapy group had a statistically significantly greater reduction in positive symptoms than the other 2 groups ($P< 0.05$). In the clozapine group, the mean positive symptom score decreased by 31% with treatment (before, 23 and after, 16; $p>0.05$); however, the reduction was not statistically significant. In the ECT group, there was a statistically significant 51% reduction in the mean positive symptoms score with treatment (before, 25 and after, 12; $P < 0.05$). In the combination therapy group, there was a statistically significant 80% reduction in the mean positive symptom score (before, 26 and after, 5; $P < 0.001$) (Table 3). With respect to the

negative symptom scores, the clozapine and combination therapy groups had a greater reduction than the ECT group, though the difference among the groups was not statistically significant. The mean negative symptom score decreased from 32 to 12 in the clozapine group ($P < 0.05$), from 33 to 13 in the combination therapy group ($P < 0.05$), and from 31 to 22 in the ECT group ($P > 0.05$) (Table 3) .

Table 2. Mean total PANSS scores before and after treatment by treatment group.

Treatment Group	Mean PANSS score before treatment	Mean PANSS score after treatment	P Value
Clozapine	95	52	0.001
ECT	99	60	0.001
Combination therapy	99	29	0.001

Table 3. Mean positive symptoms scores before and after treatment by treatment group.

Treatment Group	Before treatment	After treatment	P
Clozapine	23	16	0.1
ECT	25	12	0.05
ECT+ clozapine	26	5	0.001

During treatment, the combination therapy group had no severe, unexpected side effects; the MMSE test did not reveal any cognitive complications in any of the patients.

DISCUSSION

The results of this study demonstrate that combination therapy with clozapine and ECT is more effective than either treatment alone for the treatment of treatment-resistant schizophrenic patients. Our results are consistent with those reported by Batia and Gupta (1998), Kales and Dequardo (1999) and Kupchik and Spiva (2000). Our study also demonstrated that combination therapy produced a quicker response, as previously reported by James and Gray (1999) and Megged (2001). In the present study, none of the patients treated with combination ECT and clozapine therapy experienced serious adverse effects, which is consistent with the previous report that showed that this combination therapy is not associated with any complications. Many psychiatrists believe that, in the treatment of schizophrenia, too much attention is sometimes paid to reduction or elimination of positive symptoms, while little or no attention is paid to the negative symptoms or to the various aspects of the patients' general performance. Taking this into account, the number of treatment-resistant schizophrenic patients is actually much higher than is presently reported. On the other hand, the majority of antipsychotic drugs (particularly type one) have a greater effect on positive symptoms than negative symptoms; in fact, some have no effect on the negative symptoms (Kaplan and Sadock, 2003). Two factors likely account for the synergistic effect seen with the combination of clozapine and ECT. First, it has been observed that there is a paradoxical relationship between seizures (abnormal EEG) and psychosis (behavioral and emotional disorders) (Kaplan and Sadock, 2000). In some patients with epilepsy, psychotic symptoms and seizures occur alternately; when the patient has seizures there are no psychotic symptoms, but when the seizures are controlled, psychotic symptoms appear despite the presence of a normal EEG. The term psychosis alternative and / or forced normalization is used to describe the probable antagonism between psychosis and seizures or EEG discharges (Kaplan and Sadock, 2000). On the other hand, the combined use of ECT and clozapine induces seizure activity, and, given the antagonism between psychosis and seizure activity, this results in the reduction of psychotic symptoms. Another possible explanation for the mechanism of combined therapy with ECT and clozapine is a change in the blood-brain barrier (BBB) permeability. An increase in BBB permeability occurs following a seizure caused by ECT (Kaplan and Sadock, 2003); this leads to the passage of large molecules across blood vessels into the CNS. This allows a greater amount of clozapine to enter brain tissue without affecting tissue concentrations in other organs; thus, there is no need to use higher oral doses of clozapine. The effectiveness of clozapine is dose–dependent (a higher dose has a more benefit), but higher doses of clozapine are associated with various side effects. Thus, changes in BBB permeability as a result of ECT allow greater amounts of clozapine to enter the brain without systemic side effects. In this way, combination therapy with ECT and clozapine results in a synergistic effect. This and previous studies have shown that combination therapy with ECT and clozapine is safe and significantly better than either treatment alone in treatment-resistant schizophrenic patients. However, a limitation of this study is that the duration of remission was not studied; future studies will need to address this issue. On the other hand, treatment stability following ECT termination is not clear. In 1999, Kales Dequardo (1999)

emphasized the effectiveness of combination therapy with ECT and clozapine. In 2004, Kho and Blansjaar (2004), in their study of drug-resistant schizophrenic patients treated with ECT and clozapine, found that patients had recurrent symptoms after remission; patients were kept in remission with a maintenance dose of clozapine and weekly ECT. Thus, it could be concluded that a maintenance dose of clozapine with weekly CT could result in a short period of remission. Further follow-up studies of these patients are needed. Another limitation of this study is the small number of cases. As well, though a 2-week drug-free wash-out period was used, the long-term carryover effects of previous drug therapy cannot be completely ruled out. In recent years, combination therapy involving ECT with clozapine has been used to treat treatment-resistant type I bipolar disorder patients, particularly those in the manic phase, as well as for patients with treatment-resistant eating disorders; the preliminary studies showed promising results (Chanapaltana, 2000). Considering all of these issues and the results of the present and previous studies, combination therapy with clozapine and ECT appears to be safe and effective for all of the patients' symptoms, particularly for the negative symptoms and the patients' individual, occupational, and social functional disorders. Therefore, it is a suitable alternative for treatment-resistant schizophrenic patients.

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