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Research Article

Comparing the Effects of Mixed Treatment by Clozapine and Risperidone with Clozapine and ECT Over Patients with Clozapine Treatment-resistant Schizophrenia

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Abstract

Aim: Despite the effectiveness of antipsychotic drugs over patients with schizophrenia and the drug resistance among these patients, the need for new drug mixtures is proposed to improve their treatment. This study is aimed to determine and compare the effect of mixed treatment using clozapine and risperidone with clozapine and ECT over patients with clozapine treatment-resistant schizophrenia referring to the comprehensive psychiatric center in Taft, Yazd, Iran.

Material and Method: In this clinical trial study, thirty patients with clozapine treatment-resistant schizophrenia were randomly assigned to receive co-administration of either clozapine and risperidone (n = 15) or clozapine and ECT (n = 15). Before the intervention, both groups completed the Positive and Negative Syndrome Scale (PANSS) questionnaire. Both groups received the intervention for six sessions, 3times per week. All of the participants completed the PANSS questionnaire again after the intervention. The data obtained were analyzed using SPSS as statistical tests, chi-square, and pair T.

Results: Having compared the index differences of the PANSS questionnaire before and after the treatment over patients treated with both mixtures, it was indicated that negative symptoms were decreased more notably in the clozapine and ECT group ($P < 0.05$). The decrease in the positive symptom indices, anxiety, and depression was significantly lower in the clozapine and risperidone group ($P < 0.05$), the decrease in the scores of the PANSS questionnaire was significantly more remarkable in the clozapine and ECT group ($P < 0.05$).

Conclusion: The results of this study indicated the effect of both mixed therapies, clozapine and risperidone, and clozapine and ECT in improving the positive and negative symptoms of schizophrenia. With regards to the more significant decrease in PANSS total score in the clozapine and ECT group, more studies are to be done on this treatment.

Keywords: Clozapine; Risperidone; ECT; Schizophrenia; Resistance to Clozapine

Introduction

Schizophrenia is a progressive mental disorder characterized by mental disorders and poor emotional responsiveness over affected individuals [1]. This disorder is associated with a generally chronic and debilitating course, which causes occupational disability, personality degradation, disruption of personal, familial, and social relationships over the patients. The disease is estimated to affect about 1% of the world's population, and its prevalence is the same all over the world [2]. The latest available statistics indicate that this disorder is more prevalent than other mental disorders (i.e. 16% of all psychiatric patients). Regarding the duration of the disease and the age of the patients, schizophrenia imposes a high social and economic burden on the family and society [3]. Therefore, any action taken to control it better and faster, in addition to reducing or preventing its recurrence by lowering the number of hospitalizations, will be economically and socially feasible [4].

Schizophrenia is a combination of a group of disorders with different clinical symptoms, therapeutic responses, and courses of the disease over the patients affected [5]. Hence, this disorder is regarded as a major problem in the general health system. Considering its consequences, the development of strategies to improve and enhance therapeutic efficacy becomes necessary.

Two groups of dopamine antagonist drugs (typical antipsychotics), such as chlorpromazine and haloperidol, and dopamine-serotonin antagonist drugs (atypical antipsychotics) such as clozapine and risperidone are applied in treating schizophrenia [6,7]. Despite significant advances in the management and treatment of schizophrenia, a total of 25-30% of the patients have not responded appropriately to any common drug therapy and become resistant to their effectiveness (patient's unresponsiveness to treatment to common doses of antipsychotics, i.e. 20 mg of haloperidol per day during 6 weeks) [1,8].

The results obtained from studies on the efficacy of drug therapy over patients suffering from schizophrenia indicated that about two-thirds of patients experience positive and negative symptoms throughout their life, which indicates the present lack of adequate treatments and the necessity of designing new ones [9,10]. Therefore, schizophrenia management and treatment is a challenging problem.

One of the methods proposed for the treatment of patients with treatment-resistant schizophrenia, considered in recent years, is the mixture of risperidone with clozapine [11]. In William., *et al*. (2006), where risperidone was applied to reinforce clozapine, it was indicated that adding risperidone to clozapine did not improve symptoms in patients with severe schizophrenia [12]. However, in Kim., *et al*. (2010) patients treated with the mixture of risperidone with clozapine made great advances in their social skills [13]. InWille., *et al*. (1990), the efficacy of clozapine and electroshock over patients who received previous treatment with clozapine was evaluated. A mixture of clozapine and electroshock was proved to be effective by 72% improvement in the symptoms of schizophrenia [14]. After the publication of the results of this study, treatment with clozapine, and in some cases, Electroshock therapy (ECT) was applied for patients with treatment-resistant schizophrenia.

With regard to electroshock therapy, it is believed that the decrease in brain metabolism, occurring after seizures caused by it, is of therapeutic effects. In addition, electroshock imposes different effects on various chemical carriers the functions of which are not well defined. The difference in the functioning mechanisms between clozapine and electroshock has made them be applied over treatment-resistant cases [11]. Hence, the combinatory use of clozapine and electroshock is one of the treatments proposed for resistant schizophrenia patients in recent years with its early studies have been promising.

Numerous studies have been conducted in this regard. In Khu., *et al*. (2004), for instance, they have studied 11 schizophrenic patients who did not respond to clozapine and other antipsychotics, whereas 8 patients indicated symptoms of schizophrenia improvement after the mixed treatment with clozapine and electroshock [15]. Petrodes., *et al*. (2015), [16] and Sandip., *et al*. (2015) indicated the clozapine-enhanced treatment with electroshock is a safe and effective option [17].

Considering the above-mentioned contradictory results and the importance of clozapine treatment resistance over patients with schizophrenia, in relation to complementary therapies in curing treatment-resistant schizophrenia and the lack of enough studies to show the beneficial effect of the two mixed treatments, this study is aimed to compare the efficacy of the combination of clozapine and risperidone with the combination of clozapine and ECT.

Methods

This research is a pre and post-semi-experimental study in which the effect of mixed treatment with clozapine and risperidone with clozapine and ECT was investigated over Patients with clozapine treatment-resistant schizophrenia referring to the comprehensive psychiatric center of Taft, Yazd, Iran in 2017. The inclusion criteria to this study were: aged 15 years and older, treatment-resistant schizophrenia (based on the diagnosis of a faculty psychiatrist through clinical interviews based on DSM-IV criteria), symptoms of high-resistance treatment (more than 15 cases on the PANSS scale), lack of liver disease, lack of ECT treatment in the last

six months, absence of any systemic or chronic disease, no history of substance abuse associated with schizophrenia, lack of epileptic seizures, and willingness to participate in the study by completing the informed consent form. The exclusion criteria from this study were: the presence of depression (based on clinical interviews with regard to DSM-IV criteria), mental retardation, schizoaffective disorder, and bipolar disorder, neurological diseases (epilepsy, Parkinson's disease), ischemic heart disease, or heart failure, the use of antidepressants or lithium, medication rest, abuse of substance during the last month (except nicotine and caffeine), the presence of complications of extrapyramidal (EPS), deafness and lack of speech of the patient, the presence of active suicidal or homicidal thoughts, pregnancy, and lactation, the use of long-acting antipsychotics for less than three months, history of allergy or serious complications with the drugs studied during the research.

The investigation was started by a researcher after obtaining the necessary permits from Shahid Sadoughi University of Medical Sciences, Yazd, and obtaining permission from the officials of the comprehensive psychiatric center. To this end, the researcher began the study after confirming the criteria for entering it and obtaining written informed consent for the willingness to participate. The information-gathering tool in this research was the Positive and Negative Syndrome Scale (PANSS), which was completed by patients before the onset of the intervention according to the research objectives (evaluation of the effect of therapeutic intervention in the studied patients on the severity of symptoms as well as the evaluation of the response to treatment intervention).

After completing the questionnaires, the patients were randomly allocated into two groups treated with clozapine and risperidone (15 patients) and treated with a combination of ECT and clozapine (15 patients). Intervention in the clozapine and risperidone combination group included starting clozapine at a dose of 12.5 mg and up to a maximum of 450 mg with risperidone dose starting from 1 mg and up to a maximum of 3 mg per day for six weeks. Intervention in the clozapine and ECT combination group included starting clozapine at a dose of 12.5 mg and up to a maximum of 450 mg with ECT delivery for six sessions, 3 times per week. In order to determine and compare the efficacy of the combination therapy of clozapine and risperidone with combination therapy of clozapine and ECT over patients with schizophrenia resistant to clozapine treatment, six weeks after the intervention, patients again completed the PANSS. Positive and Negative Syndrome Scale (PANSS) included 30 questions in 5 dimensions: negative symptoms (8 questions), positive symptoms (6 questions), interruptions (7 questions), anxiety (4 questions), stress and depression (5 questions) which was scored based on a five-point Likert Scale (at all: Score 1, Sometimes: Score 2, Medium: Score 3, High: Score 4, and Very High: Score 5). So the lowest score was 30, and the highest score was 150. The higher scores indicate the severity of the symptoms, so the average score was 30-70 for the severity of the low symptoms, 70-110 for the severity of the mean symptoms, and 110-150 for the severity of the severe symptoms. Validity and reliability of the Positive and Negative Syndrome Scale (PANSS) by Fisbin and Oppler (1986) were confirmed by content validity and construct validity with a Cronbach's alpha of 0.83 [18]. The Persian version of the Positive and Negative Syndrome Scale (PANSS) has been examined and validated by using factor analysis and having a Cronbach alpha of 0.80 in Abolqasemi (2007) and Gomari Givi., *et al*. [19,20]. The reduction in the PANSS score means the response to the treatment, so reducing the PANSS score further means a more favorable and comprehensive response. The questionnaire was completed by a psychiatrist's assistant who was not informed about the type of treatment (one-blind study). After coding the two-step data and entering the data, SPSS software version 18 was used for analysis using Chi-square, independent T-test, Wilcoxon test, and other descriptive and analytical statistical methods, and the changes after the six weeks in each group and between the two groups were compared and reported at 95% confidence level ($P \leq 0.05$).

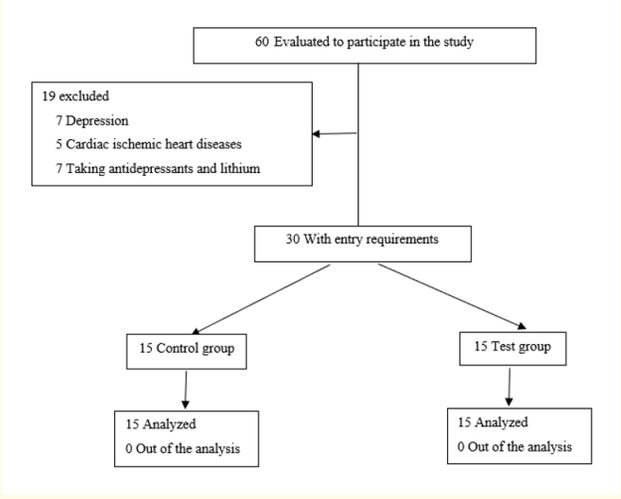

Figure 1: Participant flow in the study.

Results

In this semi-experimental study, 30 patients with schizophrenia resistant to clozapine treatment (15 patients treated with risperidone and clozapine, and 15 patients treated with clozapine and ECT) were participating in this study who referred to the comprehensive psychiatric center of Taft, which had inclusion criteria,

of which 21 of the subjects were male (70%), and 9 (30%) were women. The minimum and maximum ages of patients were 22 and 59 years, respectively. There was no significant difference in age and sex in the two groups (P ≤ 0.05). Table 1 shows the information about the variables of the Positive and Negative Syndrome Scale (PANSS) before and after treatment in two groups. Comparison of mean scores of negative symptoms index before and after treatment by the studied groups showed; mean score of negative symptoms index was 30.07 ± 5.24 before treatment in the clozapine and risperidone group, which changed after six weeks of treatment intervention, mean reduction was 27.4 ± 5.12 (reduction was 2.67 ± 0.12). The mean score of the negative symptoms index before treatment in the clozapine and ECT group was 28.07 ± 7.23, which was 22.73 ± 4.83 after six weeks of treatment (reduction was 5.34 ± 2.4). The results showed a statistically significant difference in the negative symptoms index over patients with clozapine and ECT before and after treatment (P < 0.05). Also, the results of the evaluation of positive symptoms index before and after treatment in both groups showed that the mean score of this index before treatment in the clozapine and risperidone group was 16.67 ± 3.85, which was changed to 14.87 ± 3.52 after treatment (reduction of 1.8 ± 0.33). The mean score of positive symptoms index was 14 ± 3.78 before treatment in the clozapine and ECT group. This index was 13 ± 2.59 after treatment (reduction was 1 ± 1.19). The decrease in the positive symptoms index in the clozapine and risperidone group was more pronounced (P < 0.05).

The analysis of the interruption index before and after treatment in both groups showed that the mean score of interruption index was 15.8 ± 3.9 before treatment in the clozapine and risperidone group. This index was 13.2 ± 2.2 after the treatment (reduction was 2.6 ± 1.7). The mean of this index was 19.93 ± 2.66 in the clozapine and ECT group. After the treatment, this index was 14.07 ± 2.8 (reduction was 5.86 ± 0.14). The results showed a significant difference between the patients in the clozapine and the ECT group before and after the treatment (P < 0.05) so that the reduction of the interruption index in the clozapine and ECT group was more significant. The evaluation of stress and depression index before and after treatment showed that the mean score of this index was 6.67 ± 1.72 before treatment in the clozapine and risperidone group, which reached 5.6 ± 0.83 after treatment (reduction was 1.07 ± 0.89). The mean score of stress and depression index was 6.47 ± 1.73 before treatment in the clozapine and ECT group. After treatment, this index reached a mean of 5.53 ± 0.83 (reduction was 0.94 ± 0.9). Significant statistical differences were observed in patients in the clozapine and risperidone group before and after treatment (P <0.05) so that the reduction in stress and depression score in the clozapine and risperidone group was more significant. The results of the total score scale study of positive and negative symptoms of PANSS schizophrenia before and after the treatment showed that the mean total score of PANSS scale before treatment in the clozapine and risperidone group was 78.53 ± 12.46 which was 68.27 ± 9.82 after the treatment (reduction was 10.26 ± 2.64). The mean total score of this questionnaire before treatment was 80.2 ± 13.7 in the clozapine and ECT group, which was 63.47 ± 9.19 after the treatment (reduction was 16.73 ± 4.51). The result showed a statistically significant difference of this index between the patients in the clozapine and the ECT group before and after treatment so that the decrease in the total score of PANSS scale in the clozapine and ECT group was significantly higher (Table 2).

Group	Time of review	Before treatment	After treatment	Test Result
Negative symptoms	Clozapine and risperidone	30.07 ± 5.24	27.4 ± 5.12	P < 0.001
	Clozapine and ECT	28.07 ± 7.23	22.73 ± 4.83	P = 0.001
	Test result	P = 0.285	P = 0.007	-
Positive symptoms	Clozapine and risperidone	16.67 ± 3.85	14.87 ± 3.52	P = 0.007
	Clozapine and ECT	14 ± 3.78	13 ± 2.59	P = 0.09
	Test result	P = 0.055	P = 0.089	-
Interruption	Clozapine and risperidone	15.8 ± 3.9	13 ± 2.2	P = 0.001
	Clozapine and ECT	19.93 ± 2.66	14.07 ± 2.8	P = 0.001
	Test result	P = 0.006	P = 0.367	-
Anxiety	Clozapine and risperidone	9.33 ± 2.77	7.4 ± 1.7	P = 0.001
	Clozapine and ECT	11.73 ± 3.9	7.13 ± 1.12	P = 0.001
	Test result	P = 0.902	P = 0.089	-
Stress and depression	Clozapine and risperidone	6.67 ± 1.72	5.6 ± 0.83	P = 0.007
	Clozapine and ECT	6.47 ± 1.73	5.53 ± 0.83	P = 0.031
	Test Result	P = 0.683	P = 806	-

Table 1: Comparison of Positive and Negative Scale (PANSS) scores in patients before and after treatment.

	Before treatment	After treatment	Test Result
Clozapine and risperidone	78.53 ± 12.4	68.27 ± 9.82	P < 0.001
Clozapine and ECT	80.2 ± 13.7	63.47 ± 9.19	P < 0.001
Test result	P = 0.713	P = 0.081	-

Table 2: Comparison of the total score of the PANSS questionnaire in patients before and after treatment.

Discussion

The results of this study showed that the reduction in the mean score of negative signs indices, interruption, and anxiety of the Positive and Negative Syndrome Scale (PANSS) was significantly more pronounced in the patients treated with clozapine and ECT than in the clozapine and risperidone group (P < 0.05). The decrease in the mean scores of positive symptoms, stress, and depression indices in the PANSS scale in the clozapine and risperidone group showed a significant decrease (P < 0.05) compare to patients treated with clozapine and ECT. According to the results of this study, combination therapy of clozapine and ECT has been effective in reducing the negative symptoms, interruption, and anxiety in patients resistant to clozapine treatment and combination therapy of clozapine and risperidone in reducing schizophrenia symptoms in patient's resistance to the clozapine treatment have had a significant impact. The results of Samadi., *et al*. (2017) showed that combined ondansetron with risperidone was associated with a significant reduction in PANSS scale total score and negative symptoms and interruption indices as compared to the group treated by the combination of risperidone and placebo (p > 0.05). Also, there was no difference between the two groups receiving ondansetron and risperidone, and the combination of risperidone with placebo in the anxiety and depression index in the post-intervention period (P < 0.05) [21]. The results of this study were inconsistent with the results of our study. In the study of Samadi., *et al*. ondansetron and risperidone have been used as a therapeutic approach that ondansetron, as a serotonin receptor antagonist (5-HT3), is more effective in enhancing cognitive function and reducing negative symptoms of schizophrenia than other symptoms [22-24].

The results of a study by Kelly., *et al*. (2015) showed that only 30% of patients had improvement in the positive and negative symptoms of PANSS in the two groups receiving clozapine and minocycline. However, there was a significant improvement in depression and anxiety in the clozapine and minocycline group (P < 0.05) [25]. The results of this study were in agreement with the results of the present study, regarding the improvement of the anxiety and depression index of the PANSS scale, however, in terms of the lack of improvement in the indicators of positive and negative symptoms, the interruption and incontinence, it was not consistent with the results of our study. Minocycline has glutamate activity and modulator and promotes neuronal activity in response to increased GABA receptors [26]. Therefore, considering the type of minocycline activity in the nervous system, improvement in anxiety and depression symptoms in schizophrenic patients can be expected. The results of Muscatello., *et al*. (2014) showed that the group receiving clozapine combined with ziprasidone showed a significant decrease in the positive and negative symptoms of the PANSS scale (P > 0.05). Also, the mean change in scores of each of the five PANSS scores in the combination treatment group of clozapine and ziprasidone showed a significant difference compared to the pre-intervention period (P > 0.05) [27]. The results of this study coincided with the results of our study. A similar function of ziprasidone as an atypical antipsychotics drug in combination therapy with clozapine can be seen in reducing the symptoms of both positive and negative symptoms, interruption, anxiety, and depression in patients who are resistant to treatment. The results of the study by Petridis., *et al*. (2015) showed that out of 39 patients, 19 patients (48.7%) had a 40% reduction in their psychological symptoms after eight weeks of study. There was no significant difference in terms of improvement of negative symptoms between the intervention and control groups (P > 0.05) [28]. The results of this study were non-consistent with the results of our study. The reasons for the difference in results are the number of samples (39 versus 30 patients with refractory schizophrenia), as well as the longer study period (eight weeks versus six weeks of treatment intervention) in this study compared to our research. The results of Gul., *et al*. (2014) showed that in the ECT and clozapine groups, the mean scores of each of the indices were lower than that of the risperidone recipient alone (51.11 vs. 56.35) [29]. The results of this study were in line with the results of our study, with the difference that the positive symptoms in our study before and after the intervention were not different significantly. Among the reasons for not matching the results of this study, we can refer to the duration of the study (nine months versus six weeks). Also, during the intervention period in this study, the dose of ECT in patients varied according to their age, which could affect the outcome of the study. The results of the study by Garg., *et al*. (2012) showed a significant change in the mean score of PANSS scale in the ECT and clozapine treatment groups compared to the clozapine recipient group (P < 0.05) so that during the six weeks study, the mean scores of this scale were improved in the test group (70.7 at baseline and 65.6 at the end of the study) [30]. The results of this study were in line

with the results of our study that was due to the similarity of the intervention method, the type of intervention, the duration of the drug, and the similar dose of the two studies.

Generally, antipsychotics are the basis of the clinical management and treatment of patients with schizophrenia that despite the effectiveness of this drug group, there are some health problems, such as drug resistance in patients with schizophrenia [31]. According to the results of the studies, new drug compounds appear to be necessary to eliminate drug resistance. But according to the results of some studies, the treatment responses to the evaluated drugs are different, and more effective drug treatment with consideration of their side effects is a challenge for the treatment of these patients. In the case of electroshock (ECT), although its exact mechanism of action is unclear, it is believed that a decrease in brain metabolism that occurs after seizures has a significant therapeutic effect on the symptoms of schizophrenia. In addition, electroshock has different effects on different chemical carriers that are not well defined. The different mechanism of action of clozapine and electroshock has led to the use of schizophrenia in cases of resistance to treatment [4,5,32]. The results of this study showed the beneficial effects of combination therapy of clozapine and ECT in reducing negative symptoms, interruption, depression, and anxiety in patients with schizophrenia resistant to treatment. In the present study only in the positive symptoms index, the control group did not change the mean scores of positive symptoms of PANSS scale compared to the period before the intervention this group, it seems that the negative symptoms are a component of the patient's depression, which gives rise to a quick response to ECT therapy.

Conclusion

According to the results, combination therapy of clozapine and risperidone and combination therapy of clozapine and ECT has been effective in any of the PANSS scale indices, however, the clozapine and ECT combination therapy resulted in a further decrease in the mean scores of PANSS scale versus the clozapine and risperidone combination therapy. Therefore, the ECT and clozapine combination therapy by taking into account the significant effect of it on the symptoms of patients resistant to clozapine treatment, especially the negative symptoms and functional impairment of the patient, in the individual, occupational and social fields, can be considered a suitable alternative therapy for schizophrenia patients who are resistant to the treatment.

Ethical Considerations

This study is based on the dissertation of the psychiatric specialty and taken from research project number 5446, which was approved by the ethics committee of Shahid Sadoughi University of Medical Sciences. Written consent was received from the participants before entering the study. Explanation on how the research was carried out was presented to samples and their fellows and they were allowed to leave the study at any stage.

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