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The Comparison of the Effectiveness of Thiothixene and Risperidone as a Combination with Lithium for the Treatment of Patients with Bipolar Disorder

Nooshin Parvaresh,[1] Hasan Ziaadini,[2] Shahrzad Mazhari,[1] Maryam Fazli*[3]

1. Kerman Neuroscience Research Center, Department of Psychiatry, Kerman University of Medical Sciences, Kerman, Iran
2. Department of Psychiatry, Kerman University of Medical Sciences, Kerman, Iran
3. Resident of Psychiatry, Kerman University of Medical Sciences, Kerman, Iran

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*Corresponding author at:
Resident of Psychiatry, Kerman University of Medical Sciences, Kerman, Iran.
E-mail:
fazlim62@yahoo.com

Abstract

***Background*:** The effectiveness of various atypical antipsychotics in the treatment of acute mania is reported repeatedly, but those for typical antipsychotics are restricted to haloperidol and chlorpromazine. As there is a comparative importance of side effects for typical and atypical antipsychotics, we decided to compare the therapeutic effect of thiothixene and risperidone as a combination with lithium for the treatment of patients with bipolar disorder.

***Materials and Methods*:** In 8 week double-blind clinical trial, 84 patients with a diagnosis of bipolar disorder were randomized for treatment with lithium plus thiothixene (N=42) or lithium plus risperidone (N=42). Manic, positive-negative symptoms, anxiety and depression were measured bi-weekly with Young Mania Rating, positive and negative symptom scale (PANSS) and Hamilton rating scale score. Fasting blood sugar, weight, general side effects and extrapyramidal symptoms were also evaluated. The measures analyzed using SPSS-17 software. To compare demographic characteristics *t*-test, χ^2 test and fixed effects method were used. A fixed effects method was applied to omit missing data effects.

***Results*:** There was no significant difference between the thiothixene and risperidone groups in Young mania rating scale and other outcome measures during the 8 week trial. There was no significant difference in weight, blood sugar and clinical global impression (CGI) between groups.

***Conclusion*:** Thiothixene is as effective as risperidone in the improvement of manic and psychotic symptoms. There was no significant difference with risperidone in developing extrapyramidal symptoms, so it can be used as an appropriate combination with lithium for the treatment of bipolar patients in psychotic manic episode.

Introduction

Bipolar disorder consists of at least a period of mania, hypomania or mixed. The prevalence of bipolar disorder is 5% of public [1]. Mania is the main form of bipolar disorder. Mood stabilizers such as lithium and valproate are used as the first line in the treatment of acute mania [2-4]. But, studies have shown that in most patients who were treated by lithium or sodium valproate for more than 3 weeks, manic symptoms would not remitted completely. As the rapid control and remission of acute mania is important, the combination of medications are used widely [5].

Many studies have compared the therapeutic effects of typical and atypical antipsychotics in the treatment of bipolar disorder patients. In a metaanalysis by Copriani et al. haloperidol was one of the most effective antimanic medications in comparison with asenapine, aripiprazole, quetiapine and ziprasidone, but did not differ in effectiveness with risperidone and olanzapine [6].

In Sachs et al. study, risperidone or haloperidol in combination with a mood stabilizer was more effective than placebo and mood stabilizer, and there was no difference between risperidone and haloperidol in Young mania rating scale score and CGI, but with more extrapyramidal symptoms in haloperidol group [5]. In Scherk et al. meta-analysis, atypical antipsychotics and haloperidol were compared. The result showed that the decrease in manic symptoms with aripiprazole and risperidone was similar to haloperidol, but in olanzapine and quetiapine groups the improvement in Young mania rating score was significantly less in comparison with haloperidol [7]. Another metaanalysis was done by Yildiz et al. on 38 monotherapy studies, in which 56 placebo-medication trials on 10,800 manic patients were compared, and finally could not find any significant differences between haloperidol and atypical antipsychotics [8].

As in most studies haloperidol has been chosen as typical antipsychotic [9] in this study, thiothixene is compared with risperidone in a combination therapy with lithium. Thiothixene is a thioxanthine antipsychotic and is similar to group III of phenothiazins like fluphenazine [10, 11]. This is the first study of the effectiveness of this antipsychotic in the improvement of manic, psychotic, depression and anxiety symptoms in patients with bipolar

disorder type I. Furthermore, the prevalence of side effects as extrapyramidal, weight gain and increase in blood sugar are compared in both groups. So far, many studies have investigated the effectiveness of atypical antipsychotics in the treatment of acute mania, and most of them have been evaluated in different trials, but for typical antipsychotics, studies are restricted to haloperidol and chlorpromazine. According to side effects, two drug groups differ from each other. So, this study can be helpful to evaluate the therapeutic effect of thiothixene as a typical antipsychotic in treatment of patients with bipolar disorder.

Materials and Methods

The study is a randomized clinical trial. Eighty-four patients between 18 and 60 years old were entered the study; they were hospitalized in Shahid Beheshti psychiatric hospital, Kerman, with impression of bipolar disorder (manic or mixed phase) by two psychiatrists based on DSM-IV-TR. Before starting the study, written consent had been completed by the patient's family or relatives and the aim of the study were explained. Demographic data was recorded. Eighty-four patients were randomized for treatment of risperidone+lithium (N=42) or thiothixene+lithium (N=42). The including criteria were the score above 20 in Young mania rating scale, age (18-60) and diagnosis of bipolar disorder according to DSM.

Patients with medical diseases such as diabetes (fasting blood sugar above 110), epilepsy, mental retardation and those who received psychotropic drugs within 4 weeks before the study were excluded. The improvement was considered 50% decrease in Young mania rating scale score and positive and negative symptom scale (PANSS) in the last visit (8th week). Thiothixene and risperidone were packed in two packages with the code of A and B by the pharmacist and were sent to the ward by the order of psychiatric resident. Lithium carbonate was started by 900 mg/day for every patient. Thiothixene was started 5 mg/day (one capsule) and increased according to the patient's clinical response up to 15 mg/day. Risperidone was started 2 mg/day (one tablet) and based on the patient's clinical response increased up to 6 mg/day. The dose has been decreased with intolerable side effects in each group. The psychiatric resident was blind for the type of the medication.

In the case of insomnia lorazepam (1-2 mg), extrapyramidal symptoms anti cholinergic (biperiden) and for severe agitation propranolol were prescribed. This study lasts 8 weeks and patients were evaluated 5 times (at baseline and every 2 weeks). The instruments for evaluation were: Young mania rating scale, PANSS and Hamilton rating scale in 0th, 2nd, 4th, 6th, 8th week, general side effects and extrapyramidal symptoms in 2nd, 4th, 6th, 8th week. Fasting blood sugar, weight and CGI were measured in 0th and 8th week. Young mania rating scale consists 11 questions. This questionnaire has acceptable reliability and validity and can be used in clinical trials and researches. The concurrent validity of Young mania rating scale was 87%, for the first evaluator 89% and 84% for the second [12]. Hamilton depression rating scale has 24 elements with correlation coefficient of 65% and 66% and reliability of 89%, the Hamilton anxiety rating scale has 14 elements with correlation of 75% and reliability of 85%. PANSS was used to evaluate symptoms and dimensions of schizophrenia. This scale consists 30 elements and a completely defined method which can be administered to evaluate the positive, negative and other symptoms based on semi structured and formal clinical interview. Three supplementary elements are added at the end to study the possibility of aggression [13]. Clinical Global Impression (CGI) which is recorded before treatment and at the end is ranked from 1 (no sickness), 2 (very minimal), 3 (minimal), 4 (mild), 5 (significant), 6 (sever) and 7 (so sever) [14].

Drug side effects questionnaire consists of 16 questions which are scored between 0-4. Extrapyramidal symptoms check list consists 7 parts. The first to seventh parts is scored: 0-36, 0-66, 0-40, 0-28, 0-8, 0-8 and 0-5. The length of hospitalization was at least 2 weeks and all patients who were hospitalized entered analysis. The patient could leave the study whenever they desired. The psychiatric resident was 24 h on call to solve the probable problems in patients.

For statistical analysis SPSS-17 was used. In order to compare the demographic data between two groups, *t*-test was used for quantitative variables and χ^2 test for qualitative ones. To compare the effectiveness of risperidone and thiothixene and to omit the effect of missing data, mixed effects models were used. For post-hoc analysis, student *t*-test was applied. p-value<0.05 was considered significant.

Results

The study flow chart is shown in figure 1. There was no statistically significant difference between age, sex, duration of illness and the age at first hospitalization. The mean of episode numbers in risperidone group was 4.6 and in thiothixene was 4.5. The mean of lithium level in risperidone group was 0.59 meq/L and in thiothixene was 0.64 meq/L, which was not significantly differed between two groups. The rate of improvement was considered 50% decrease in Young mania rating score and PANSS in the last visit (8th visit). To investigate Young mania rating score in two groups of risperidone and thiothixene, there was statistically difference in both groups during the study ($p<0.001$), but there was no significant difference between two groups (Fig. 2). According to PANSS score in two groups there was statistically significant difference in each group during the study, but there was no significant difference between two groups. In Hamilton depression scale score there was no statistically significant difference between groups.

The rate of extrapyramidal symptoms during the study in groups was significant ($p=0.007$). In thiothixene group the rate of extrapyramidal symptoms was more, especially in the fourth week, but the difference between two groups was not statistically significant (Fig. 3).

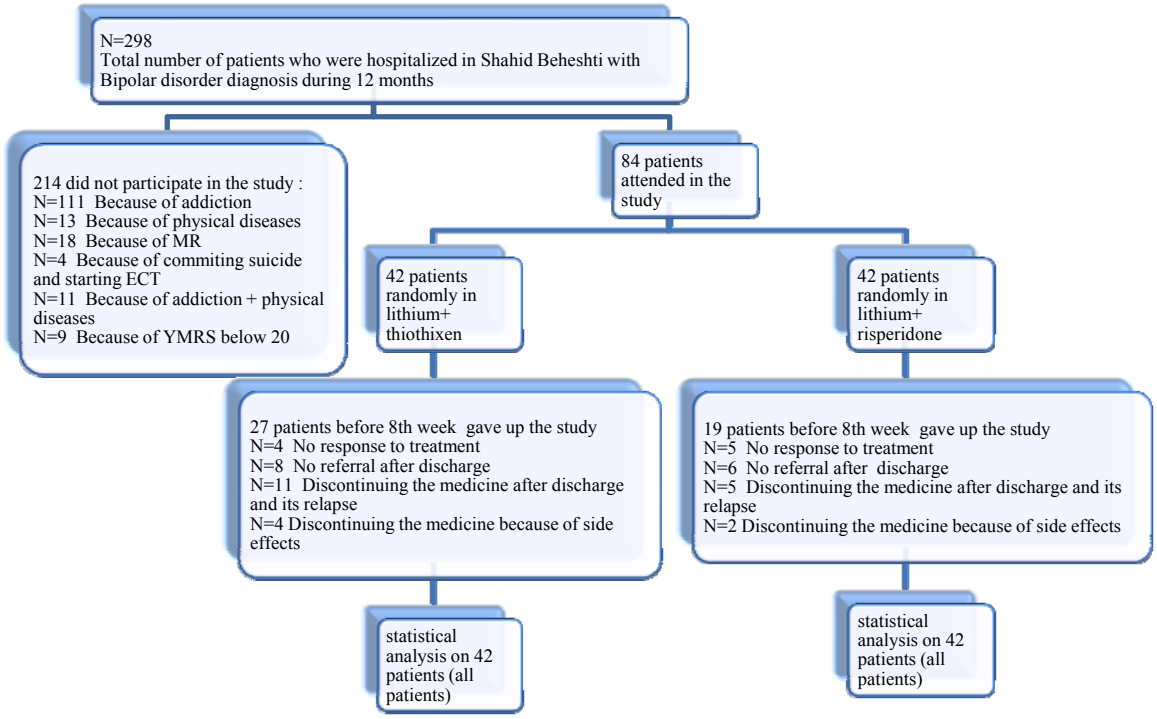

Figure 1. Trial's flow chart

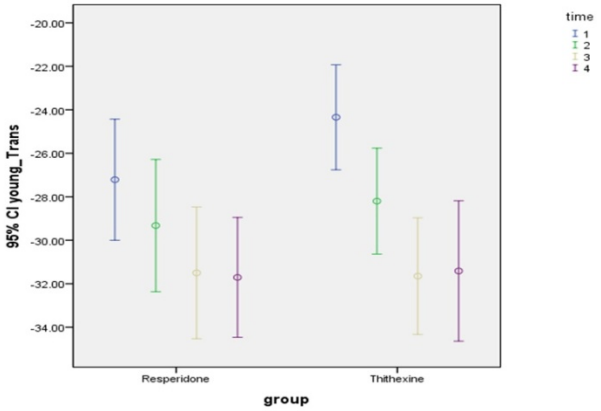

Figure 2. The comparison of changes in Young mania rating scale score between 2 groups

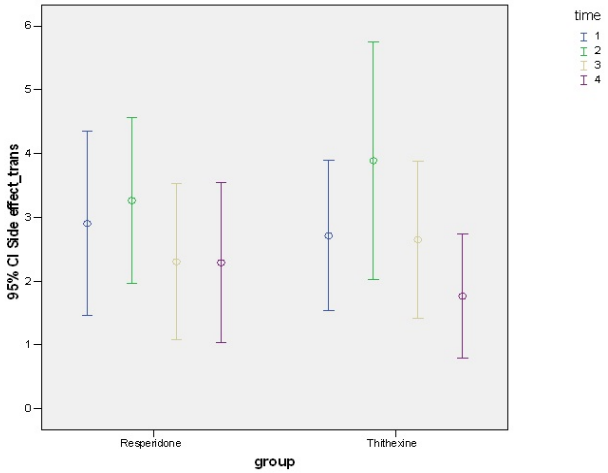

Figure 4. The comparison of changes in the rate of side effects between two groups

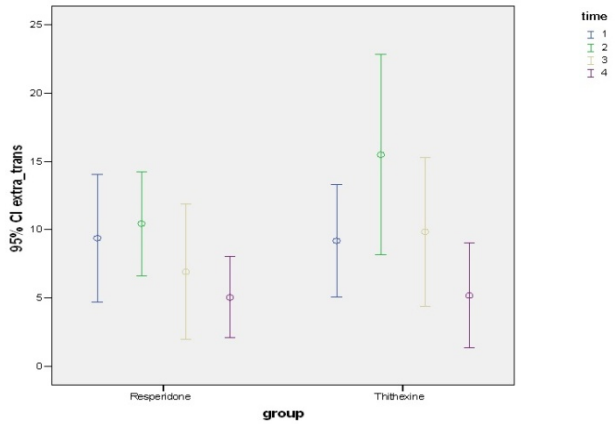

Figure 3. The comparsion of changes in extrapyrasmidal symptoms questionnaire score between two groups

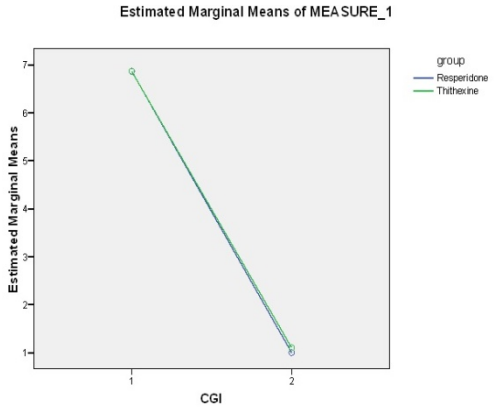

Figure 5. The comparison of changes in CGI between two groups

In thiothixene group more general side effects were observed specially in the fourth week, but these changes were not statistically significant in groups during the study and between groups, either (Fig. 4). Fasting blood sugar was not significant in and between two groups. The change in patients' weight during the study was significant in each group ($p<0.001$), as both groups has weight gain but no significant difference was present between two groups. CGI change was significant in both groups ($p<0.001$) but there was no statistically significant difference between them (Fig. 5).

In spite of more dropout rate in thiothixene group, and discontinuing of medication in 4 cases in this group in comparison to two cases in risperidone group because of side effects, there was not statistically significant difference. In risperidone group, the number of patients who received biperiden (1-4 mg) was 16, propranolol (10-40 mg) was 5 and lorazepam (1-2 mg) was 20. In thiothixene group, the number of patients who received biperiden (1-4 mg) was 20, propranolol (10-40 mg) was 4, and lorazepam (1-2 mg) was 21, regarding the dosage of this medication, no significant difference existed between groups.

Discussion

Based on the findings of this study, risperidone and thiothixene had the same improvement profile for manic and psychotic symptoms. There was no statistically significant difference according to depression, anxiety symptoms and extrapyramidal symptoms between two therapeutic groups.

Similar studies that compared the effectiveness of typical and atypical antipsychotics in manic patients showed the similar effect in decreasing manic symptoms [5, 6, 8], which correlates the result of this study. Although in the meta-analysis by Scherk et al., it was concluded that the decrease of manic symptoms with aripiprazole and risperidone was similar to haloperidol but in olanzapine and quetiapine groups the improvement in Young mania rating was significantly less than haloperidol. There was no statistically significant difference between the patients who were treated with atypical antipsychotic and those with haloperidol in Young mania rating [7], although in all studies the prescribed typical antipsychotic was haloperidol. Meanwhile, these studies have not compared the rate of decrease in psychotic symptoms.

There was neither significant difference in anxiety and depressive symptoms in groups during 8 weeks of treatment, nor between groups. Similarly in Scherk et al. study there was no difference between those who received haloperidol and risperidone which correlates the finding of this study [7].

The extrapyramidal symptoms in thiothixene group were more in comparison with risperidone in the fourth week but this difference was not statistically significant. Most of similar studies have shown more extrapyramidal symptoms for typical compare with atypical antipsychotics [5, 7]. This difference can be due to smaller sample size in the present study than similar studies, more potency for haloperidol in contrast to thiothixene and more extrapyramidal symptoms based on more adherence to dopaminergic receptors (D2) for haloperidol that has been chosen as typical antipsychotics in other studies.

Fasting blood sugar did not have any significant changes in either group. Weight changes had increasing process in both groups but with no significant difference between groups. Although the rate of hyperglycemia following receipt of risperidone was reported less in comparison to other atypical antipsychotics [15], because of measuring weight and fasting blood sugar in 0th and 8th week in this study and high dropout rate which nearly 50% of patients successfully finished the 8th week, the sample size was low to evaluate the difference between two groups. Weight gain in thiothixene group was the same as risperidone; it was predictable because both groups received lithium. Although in Scherk et al. study the rate of weight gain in risperidone branch was not more than haloperidol branch [7]. CGI is decreased in both groups, but there was no significant difference between two groups.

Sachs et al. study did not report any significant difference between atypical antipsychotics and haloperidol [5] which correlates the present study. This study concludes that thiothixene as a typical antipsychotic has antimanic effects on patients with bipolar disorder in addition to antipsychotic effects and its effectiveness is comparable with risperidone. The present study is the first study to compare the effect of thiothixene in a controlled study with risperidone. It seems that thiothixene has better side effect profile in comparison with haloperidol that needs more studies with larger sample size to be approved.

Other strengths of this study was its 8 weeks follow ups which was more than most similar studies which last 3 weeks, the comparison was in wider domains in addition to mania and CGI, both groups received lithium as a mood stabilizer and its blood level was compared between groups [5, 7] which did not regard in similar studies so caused the omission of one of the interfering variable.

Among the limitation were low sample size and high dropout rate. One main reason of discontinuing was being resident of out of Kerman for most patients who had far way to come for biweekly follow up visits. Risperidone and thiothixene had similar effect in mania and psychosis improvement. According to depressive, anxiety and extrapyramidal symptoms, there was no statistically significant difference between two groups.

As prescription of atypical antipsychotics such as risperidone is limited because of metabolic side effects and on the other hand, extrapyramidal symptoms are much more frequent with haloperidol than atypical antipsychotics, thiothixene can be an appropriate choice in such patients because it has similar antimanic effects with risperidone and on the other hand has less extrapyramidal symptoms in comparison with haloperidol.

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Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

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