

The Therapeutic Effectiveness of Risperidone on Negative Symptoms of Schizophrenia in Comparison with Haloperidol: A Randomized Clinical Trial

Arash Mirabzadeh^{1,2,3}, Pooneh Kimiaghdam³, Farbod Fadaei^{2,3}, Mercedeh Samiei^{2,3}, Reza Daneshmand^{3*}

1. Social Determinants of Health Research Center; University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.

2. Department of Psychiatry, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.

3. Iranian Research Center for Substance Abuse and Dependence, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.

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ABSTRACT

Introduction: A number of research studies have shown that the new generation of neuroleptic medications can more effectively contribute to treating negative symptoms of schizophrenia compared with the first generation by influence cognitive functioning. The present study examined the therapeutic effectiveness of manufactured Risperidone and Haloperidol in Iran on treating the negative symptoms of schizophrenia.

Methods: This randomized clinical trial (RCT) study examined 100 hospitalized patients who met DSM-IV. TR criteria for schizophrenia were sampled at Razi psychiatric hospital in Tehran, Iran. After two weeks of stopping neuroleptic medications, the patients were randomly assigned into two groups, Risperidone and Haloperidol group. During 8 weeks of the study, baseline and weekly assessments were performed by completing brief psychiatric report scale (BPRS).

Results: Both Risperidone and Haloperidol were effective in treating the negative symptoms of schizophrenia and improvements in both groups were initiated in the second week of treatment. The most prominent response rate was the second week in Haloperidol group and the eighth week in Risperidone group but this difference was not statistically significant.

Discussion: Prescribing Risperidone or Haloperidol for treating negative symptoms of schizophrenia can be influenced by other criteria including side effects, previous treatment histories of patients and their families and a patient's or physician's preference in prescribing a medication. Studies in other countries show that Haloperidol has better therapeutic effects in treating the negative symptoms of schizophrenia in comparison with Risperidone. Further studies on the therapeutic effectiveness of Risperidone and Haloperidol are suggested.

Key Words:

Risperidone,
Haloperidol,
Negative Symptoms,
Schizophrenia.

1. Introduction

In recent decades, an increasing advancement has been observed in identifying positive, negative and cognitive symptoms of schizophrenia. Different studies indicate that negative symptoms of schizophrenia are more difficult to be treated (Tollefson et al., 1997). Negative symptoms of schizophrenia are

associated with more disruption in cognitive functioning, and lower response rates to neuroleptic medications (Fenton & McGlashan., 1998). On the other hand, therapeutic responses to the first generation of neuroleptic medications such as Haloperidol and Chlorpromazine are associated with treatment of positive symptoms of schizophrenia but cannot completely contribute to treating negative symptoms of schizophrenia (Kay & Singh, 1998). External pyramidal effects of these medications

* Corresponding Author:

Reza Daneshmand, MD Psychiatrist

Iranian Research Center for Substance Abuse and Dependence, University of Social Welfare and Rehabilitation Sciences, Koodakyar St., Daneshjoo Ave., Evin, Tehran 13337, Iran

Tel/Fax: +98 21 2218 0095

E-mail: daneshmand74@yahoo.com

produce similar negative symptoms of schizophrenia (Ghouinard et al., 1993) which are more observable especially among elderly adults (Jeste et al., 1999). A meta-analysis conducted by Davis et al. (2003) showed that some neuroleptic medications such as Olanzapine and Risperidone are associated with more appropriate therapeutic effectiveness on negative symptoms of schizophrenia (Davis et al., 2003). A study showed that 60% of negative symptoms of schizophrenic patients are treated with taking Risperidone (Sadock et al., 2005). In a study conducted by Fadaee et al. (1982), researchers schizophrenia was found as the most prevalent psychiatric disorder among hospitalized patients in psychiatric hospitals especially among chronic cases with positive history of long-term hospitalization and institutionalization (Fadaee, 1982); therefore, the high rate of schizophrenia in the community could result in a number of individual, cognitive and social impacts. In a study on the therapeutic effects of Risperidone on schizophrenic patients at Wood Bridge hospital, Singapore, Chua et al. (2001) found that Risperidone was effective in treating cognitive performances including positive and negative symptoms of schizophrenia, and also social and vocational functions (Chau et al., 2001).

In a study conducted by Hunter et al. (2001), it was found that in short and long terms, Risperidone was better compared with Haloperidol in treating the positive and negative symptoms of schizophrenia and had fewer side effects (Hunter et al., 2001). This issue is in agreement with findings of Yen et al. study (2004) in Taiwan (Yen et al., 2004) and some other studies (Glick et al., 2001; Zhang et al., 2001; Marder et al., 2003). Kumar et al. also showed similar findings in a study on the therapeutic effectiveness of Risperidone on a group of behaviors which were similar to negative symptoms of schizophrenia (Kumar et al., 2012).

However, in similar studies, Lopez et al. (1996) and Peuskens et al. (1995) did not report similar findings (Lopez et al., 1996). Observing negative symptoms of schizophrenia in some drug users such as LSD and PCP which have no strong effects on dopamine receptors display a hypothesis that serotonin has also a role in emerging schizophrenia (Ftemi, 2008).

Observing the positive effects of newer neuroleptic medications show the inhibitory effects of these medications on serotonin receptors-type 2 and dopamine receptors in comparison with earlier types of these medications and emphasize the role of serotonin in inducing the negative symptoms of schizophrenia. On the other hand, some cognitive dysfunctions including disruptions

in visual and verbal memories, motor-visual processing, and deficiencies in executive functioning are more observed in schizophrenic patients with negative symptoms which show disruptions in serotonin and glutamate (Sommers et al., 2012). In addition, specific serotonin reuptake inhibitors (SSRIs) are also prescribed to treat negative symptoms of schizophrenia (Sommers et al., 2012). This issue emphasizes the role of serotonin deficiency in emerging negative symptoms of schizophrenia and the roles of other neuro systems in emerging cognitive deficiencies. A comparison between the therapeutic effectiveness of neuroleptic medications of the first generation and the newly-manufactured ones could explain the hypothesis of testing the role of serotonin in emerging negative symptoms of schizophrenia.

However, based on our knowledge, no study has been conducted in Iran to compare the therapeutic effects of neuroleptic medications of the first generation (e.g. Risperidone) and the second generation (e.g. Haloperidol) on the negative symptoms of schizophrenia. In order to make better medical decisions for treatment of negative symptoms of schizophrenia, several studies are required to be conducted to provide more evidence-based documents in Iran. In order to partly meet this aim, the current study was conducted to examine the therapeutic effectiveness of Risperidone in comparison with Haloperidol on negative symptoms of schizophrenia.

2. Methods

2.1 Study Design and Recruitment Setting

This is a randomized clinical trial (RCT). The present cross-sectional study was conducted at Razi psychiatric hospital in Tehran, the capital city of Iran.

2.2. Study Participants

Those hospitalized males and females aged between 20-60 years who met DSM-IV.TR criteria for schizophrenia were eligible to enter the study. Those patients who were diagnosed with other psychiatric disorders including substance use, cognitive disorders, personality disorders, mental retardation or patients with severe physical disorders such as epilepsy were excluded. In that way, 100 patients were recruited as the study sample.

2.3. Study Instruments

A structured clinical interview for DSM-IV (SCID) was used to screen patients for study participation. Brief psychiatric rating scale (BPRS) was used to assess psychiatric status. BPRS has 18 items and shows

psychopathological baseline, prognosis, and therapeutic responses. The reliability of this scale was measured and approved for Iranian patients in the previous studies (Ventura et al., 1993).

2.4. Study Procedure

After meeting all exclusion and inclusion criteria, those patients who received the total score of more than 45 in BPRS were included. Of 100 patients, 34 patients were excluded because of disagreement with study participation ($n=28$), and because of unpredicted discharge from hospital ($n=6$) at baseline. Overall, the final sample included 66 male patients who completed the study. 66 patients were randomly assigned into two groups ($n=37$ in Risperidone group and $n=29$ in Haloperidol group). Consent forms were assigned by and obtained from the participants.

Using all neuroleptic medications were cancelled for the sample for two weeks (washout period).

The washout period was determined for two weeks to eliminate the effects of drugs. This two-week duration was based on international psychopharmacological references.

Oral diazepam (10 mg) was prescribed for those patients who experienced restless and insomnia. This issue is in agreement with other studies (Gleder et al., 2002) and no other medication was prescribed for the patients. After the end of washout period, the patients were randomly assigned into two randomized groups. In group 1, the patients received Risperidone (6 mg per day) and group 2 received Haloperidol (15 mg per day). A limited number of patients ($n=5$) in group 2 suffered from extra pyramidal effects and were treated with Biperidone. BPRS was weekly completed for each patient during 8 weeks of the study. After 8 weeks, the patients were discharged from treatment.

2.5. Statistical Analysis

Paired t-test was performed to compare the results of two groups (p -value=0.05). General linear model (GLM) repeated measures analysis of variance (ANOVA) was performed to examine the changes of negative symptoms of schizophrenia between the two groups during 8 weeks of treatment. In order to measure the inequities between the co variances, Mauchely's test of Sphericity, and Greenhouse-Geisser were used during performing co-variances to show the differences between the two groups.

3. Results

The mean age of the sample was 37.41 (SD=8.46) years (in the age range of 23-57 years). There were 37 patients in group 1 and 29 patients in group 2. The two groups showed no difference in cognitive symptoms (p -value ≥ 0.05).

The mean scores of cognitive symptoms was the main variable and the two types of treatments (Risperidone vs. Haloperidol) were between subject factors in data analysis. The duration of treatment (baseline assessment and 8 weeks of treatment) was within subject factors in data analysis.

In all of these statistical analyses, p value was less than 0.05. Therefore, the differences during 8 weeks of treatment were statistically significant and the two medications contributed to treating negative symptoms of schizophrenia during 8 weeks of treatment (see details in Table1 and Figure 1).

4. Discussion

Our findings showed that using Risperidone and Haloperidol for 8 weeks of consecutive treatment were associated with treating negative symptoms of schizophrenia and the only difference was in duration and the time of treatment. Haloperidol was more effective in the 2nd week and Risperidone was more effective in the 8th week of treatment. This finding emphasizes that Haloperidol can be prescribed for receiving more rapid therapeutic responses. For more prolonged therapeutic responses, Risperidone is a better therapeutic option while most studies indicate that Risperidone has a better therapeutic effectiveness on negative symptoms of schizophrenia compared with Haloperidol.

This difference between our study and other studies could be the result of several factors including different types of questionnaires, numbers of samples, and the studied cases. There are different questionnaires to assess negative symptoms of schizophrenia. In this study, we used BPRS which has been widely used in other studies. Although different scales can assess the effects of different medications on treating negative symptoms of schizophrenia but different scores can put assessment procedure in to a difficult situation. The present study was limited to male participants because of lack of hospitalized women at Razi hospital but further studies including the two genders are suggested.

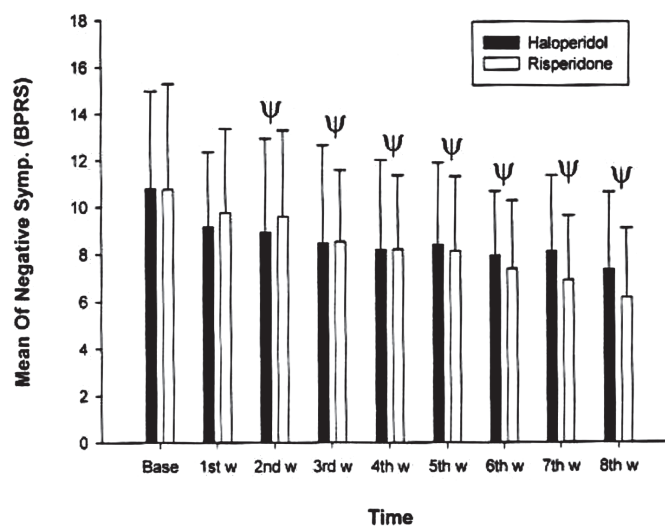
Table 1. The differences between the two groups during 8 weeks of treatment (n=66)

Duration	Group	Numbers	Mean (SD)	t	P-value
Baseline	1	37	10.76 (4.5)	0.034	0.9*
	2	29	10.79 (4.2)		
First Week	1	37	9.76 (3.6)	0.69	0.4*
	2	29	9.17 (3.1)		
Second Week	1	37	9.59 (3.7)	0.68	0.4*
	2	29	8.93 (4.0)		
Third Week	1	37	8.54 (3.0)	0.063	0.9*
	2	29	8.48 (4.1)		
Fourth Week	1	37	8.22 (3.1)	0.01	0.9*
	2	29	8.21 (3.8)		
Fifth Week	1	37	8.14 (3.1)	0.34	0.7*
	2	29	8.41 (3.5)		
Sixth Week	1	37	7.41 (2.8)	0.80	0.4*
	2	29	7.97 (2.7)		
Seventh Week	1	37	6.92 (2.7)	1.6	0.1*
	2	29	8.14 (3.2)		
Eighth Week	1	37	6.17 (2.9)	1.5	0.1*
	2	29	7.38 (3.2)		

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Using different types of neuroleptic medications could be the other reason. It is possible that Risperidone which is manufactured in Iran is different from the one which is manufactured in other countries. In this study, we used medications which were manufactured in Iran but this issue does not provide a chance to compare the results. A separate randomized clinical trial is suggested to compare the therapeutic effectiveness of neuroleptic medications manufactured in Iran in comparison with those manufactured in other countries or to compare different neuroleptic medications manufactured in different com-

panies in Iran. Since the present study could not explain this issue, therefore, designing and conducting separate studies are suggested. The prescribed dosage could be another reason for the observed difference between the two groups. The optimal dosage of prescribing Risperidone has not been globally agreed on. In this study, 6 mg of Risperidone was prescribed. In the majorities of studies, the average dosage of prescribed Risperidone is between 4-8 mg. Moller et al. (1997) reported that the optimal dose of Risperidone is 4 mg per day (Moller et al., 1997).



NEURSCIENCE

Figure 1. The trend of changes in negative symptoms in 8 weeks of treatment

Lopez et al. (1996) explained that the optimal dose of Risperidone is 8 mg per day (Lopez et al., 1996). Morder et al. (1994) explained that the optimal dose of prescribing Risperidone is 6 mg per day which can manage extra pyramidal effects (Morder & Meibach, 1994). Based on our knowledge, no study has been conducted on the best dose of Risperidone but in the present study, we prescribed the dose based on the previous studies in other countries and with an effort to prevent extra pyramidal effects.

Racial differences in therapeutic effectiveness of neuroleptic medications could be another reason. Racial differences in pharmaceutical metabolism are an important issue. No similar study on Risperidone has been conducted in Iran. Therefore, the present study can be considered as a preliminary study on this issue and further randomized clinical trials are required to be conducted on this issue in Iran.

Differences in clinical effectiveness and statistical results could be the other reason for the differences between the two groups. Previous studies are likely to report significant statistical differences that were not followed by significant clinical differences.

Volavka et al. (2002) showed that newer neuroleptic medications produce more significant statistical differences compared with earlier neuroleptic medications such as Haloperidol but this issue does not necessitate positive clinical outcomes (Volavka et al., 2002). Therefore, further studies on this issue are suggested.

It should be noted that the lack of female samples, and prescribing Biperidone for a limited number of patients whom were treated with Haloperidol were the limitations of our study. Appropriate matching of the two groups, randomly selecting the samples, being blind to the study, and having a 2 week wash out period were the positive aspects of the our study. Further studies with representative samples of both genders are still suggested.

Previous studies showed that Risperidone can be positively used in treating negative symptoms of Schizophrenia (Chouinard et al., 1993) but this issue was not observed in the present study. This issue is likely to implicate the role of neural systems engaged in inducing negative symptoms of Schizophrenia and deserves further studies.

In conclusion, in order to prescribe Risperidone or Haloperidol to treat negative symptoms of Schizophrenia, extra pyramidal side effects and patients' clinical

status should be also considered and treatment should not be only limited to treating the negative symptoms of Schizophrenia.

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