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Comparison of the Efficacy of Risperidone Made by Bakhtar Bioshimi Co. with the Risperdal Made by Janssen-Cilag Co., Belgium

Abstract

The current study aimed to compare the efficacy of risperidone made by Bakhtar Bioshimi Plant with the Risperdal made by Janssen-Cilag Co. in Belgium**.** In the current study, 22 patients diagnosed with schizophrenia who had been referred to the private offices of some psychiatrists in Isfahan were chosen as the samples based on the DSM-IV-TR criteria and inclusion criteria. These patients were divided into Iranian and Belgian drug groups (1 and 2, respectively) with a random and double-blind method, and were examined and treated for three months with a 6-mg dose of the drug on a daily and fortnightly basis.

The PANSS scale was used to evaluate the efficacy of the drugs. The SPSS Software as well as the t-test, Mann-Whitney U test, Chi-square, covariance, Pearson's, and Fisher's exact statistical test were used for statistical evaluations. The mean change of PANSS scores during the evaluation was -26.1±34.12 in Group 1 and -26.9±24.25 in Group 2. In Group 1, 66.67% of the patients have shown at least a 20% reduction in PANSS total score, and 11.11% of the patients showed at least a 60% reduction in PANSS total score. In Group 2, 53.84% of the patients have shown at least a 20% reduction in PANSS total score, and 7.7% of the patients showed at least a 60% reduction in PANSS total score. There were no significant differences between the two drugs in terms of clinical and statistical efficacy, and both drugs are similar in terms of efficacy.

Keywords: *Schizophrenia, Risperidone, Drug Efficacy, Isfahan City Psychiatrists.*

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Introduction

There are three main subjects in terms of the clinical signs and symptoms of schizophrenia: First, there are no clinical signs or symptoms specific to schizophrenia, i.e. any signs and symptoms seen in schizophrenia might be also seen in other psychiatric and neurological disorders. Second, the symptoms of each patient change over time, and Third: the training level, intelligence power, and cultural dependence of the patient should be taken into consideration. schizophrenia is a severe and chronic mental illness and its clinical syndrome is variable. Observation of the hallucinations and delusions is not necessary for the diagnosis of schizophrenia, and dysfunction (although not severe) is required during the active phase of the disease. Among the other conditions of DSM-IV-TR is that the symptoms must last at least 6 months, and the patient should not be diagnosed with schizoaffective or mood disorder (1).

Generally, schizophrenia is treated both pharmacologically and non-pharmacologically. The best results in the treatment of schizophrenia are the combination of both types of treatment (pharmacological and non-pharmacological). Clinical studies have shown that non-pharmacological treatment is less effective than pharmacological treatment, and it should not be considered a replacement for antipsychotic medication. However, the non-pharmacological treatment combined with the pharmacological treatment can lead to an increase in total medication efficacy, a reduction in the amount of required treatment, an increase in patients' participation in the treatment, and optimal occupational and social tasks (1).

Risperidone is one of the drugs used for treatment. It has a low to moderate tendency to 5-HT_{1C}, 5-HT_{1A}, and D_1 receptors, and a partial tendency to cholinergic (β_1 and β_2 adrenergic) muscarinic receptors. Also, it has a partial tendency to the adrenergic $-\beta, 5-HT_3, 5-HT_{1\beta}$ receptors, M_1, and Peptidergic receptor sites (2, 3, 4, and 5). Risperidone is distributed fast, and its distribution volume is 1-1.5 L/Kg. It binds to albumin and $-\alpha_1$ glycoprotein acid in plasma (4, 5). Risperidone and its metabolites are excreted in the urine and to a lesser extent in the feces. The average elimination half-life of the main compound and its metabolite is about 22 hours (3, 4, and 5).

PANSS is a standard tool introduced in the late 1980s to cover the shortcomings of BPRS (Brief Psychiatric Rating Scale) in the evaluation of the positive and negative symptoms of schizophrenia and other mental disorders by adding standard subjects (1, 6). It is useful for evaluation of the treatment results in the clinical studies on schizophrenia and other psychotic disorders, and includes 3 sub-scales and 30 elements: 7 elements are related to the positive symptoms, 7 to the negative symptoms, and 16 to psychopathological symptoms. Each item is scored from 1-7 based on the presence

and severity of symptoms: (1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate-severe, 6 = severe, 7 = extreme). Based on what was mentioned, the current study aimed to compare the efficacy of risperidone made by Bakhtar Bioshimi Plant with the Risperdal made by Janssen-Cilag Co. in Belgium.

Method:

In this study, the 4-mg Janssen-Cilag made Risperdal tab which was packed in 200 plastic packages was obtained from the distribution center of Daru Pakhsh Company in Tehran. The 4-mg Iranian-made risperidone tabs by Bakhtar Bioshimi Plant located in Kermanshah were chosen from the first batch packaged in 3 large plastic bags. The samples were extracted from different spots of each bag as about 1000 tabs from each and a total of 3000 4 mg tabs were obtained. To create a blinding condition for the study, the tabs were placed in a capsule. Lactose powder was used as a filler to fill the space around the tab in the capsule and to separate 2 mg tabs from the 4 mg ones, blue-colored capsules were used for the 2 mg samples and red-colored capsules were used for the 4 mg samples.

The patient was referred to the office to take the medication every two weeks, but in the cases in which the distance between the patient's living place and the location of the study was long, the drugs would be given to him/her for two weeks. The patent received 7 blue capsules (2 mg) in a small plastic bag for one week. And in the second week, bringing the bag from the last week, he/she received 7 red capsules (4 mg) for another week. In the third week also, bringing the bag that contained the drugs from the last week, he/she received 7 red and 7 blue capsules (total of 6 mg), and this procedure continued until the end of the study.

The study was done as a triple-blind randomized controlled clinical trial on the patients referring to the psychiatric wards and clinics under the supervision of Isfahan University of Medical Sciences. The washout period was 14 days and the study duration was 12 12 weeks. The patients were randomly divided into two groups. One group received risperidone made by Bakhtar Bioshimi Co. and the other received Risperdal made by Janssen-Cilag in Belgium. During the study, the recovery course and side effects were recorded by the use of clinical interviews and PANSS and AIMS questionnaires (7).

The clinical assessment was done at the baseline and continued fortnightly until the end of the 12th week. The PANSS scales which are validated in Iran have been used for evaluation of the efficacy (8). To compare the durations of illness between the two groups, the t-test has been used. Also, the Chi-square has been used to compare the demographic data (gender, marital status, employment status) between the two groups. The Mann-Whitney U test was used to compare the education level of the two groups. Also, the Pearson's and Chi-square tests were used to compare the type of diagnosis. Paired t-test was used to compare the values of each group in the baseline and the endline of the study. Finally, Covariance was used to compare the mean changes between the two groups.

Findings:

The demographic data of 22 patients (Group 1: 9 patients, and Group 2: 13 patients) who finished the trial, are provided in Table 1:

Table 1: Demographic data

Variable	N	Group 1	N	Group 2	p-value
Average age per year S.D±	9	۲۴ / ۸۹ ± ۹ / ۰۲	13	۲۴ / ۳۸ ± ۷ / ۲۶	0/886
Male : gender n and%	8	%88/9	9	%69/2	0/36
Female	1	%11/1	4	%30/8	
Married : marital status n and%	2	%22/2	2	%15/4	1
Single	7	%77/8	11	%84/6	
employed : employment status n and%	3	%33/3	1	%7/7	0/264
unemployed	6	%66/7	12	%92/3	
illiterate : educational status n and%	0	0	0	0	0/729
primary school	3	%33/3	2	%15/4	
secondary school	2	%22/2	5	%38/5	
	3	%33/3	5	%38/5	
	1	%11/1	1	%7/7	
	9	۳۳ / ۸۹ ± ۴۶ / ۲۷	13	۴۳ / ۳۱ ± ۴۶ / ۸۶	0/646
	4	%44/4	7		0/770

high school	0	0	0	%53/8	
academic	0	0	1	0	
Duration of illness per month	3	%33/3	3	%7/7	
Paranoid : type of diagnosis n	2	%22/2	2	%23/1	
and%	4	%44/4	3	%15/4	0/376
catatonic	5	%55/6	10	%31/8	
Hebephrenic	9	۱۰۲ / ۱۱ ± ۲۹ / ۵۳	13	%76/9	
Undifferentiated				۱۰۲ / ۳۸ ± ۹ / ۸۳	
Residual					
yes : smoking n and%					
No					
PANSS total score					

The patients were initially comparable in both groups, in all traits including the average age, gender, marital status, employment status, educational status, the average duration of illness, type of diagnosis, being smoker or non-smoker, total PANSS score, and their were no significant differences between the two groups.

In both groups, the number of men, the singles, the unemployed, and the non-smoker patients was higher. The patients in both groups were literate and most of them had finished high school. The most frequent types of diagnosis in both groups were paranoid, undifferentiated, and residual, respectively. The baseline total PANSS scale score shows a moderate severity of illness in both groups. although Group 2 had scored partially higher, there was no statistical difference between the two groups.

The changes observed in the evaluation of the patients by the use of the PANSS scale are presented in Table 2.

Table 2: Change in PANSS score

Tools	Group		Baseline		Endline		Changes		P-Value	
		N	Mean	S.D.	Mean	S.D.	Mean	S. D.	Intra-group	Inter-group
PANSS total score	1	9	102/1	29/53	76	16/25	-26/1	34/12	0/05	0/954
	2	13	103/4	9/83	75/5	24/84	-26/9	24/25	0/002	
PANSS positive score	1	9	21/6	8/29	13/9	3/75	-7/7	8/51	0/027	0/693
	2	13	21/5	5/94	14/8	6/96	-6/7	4/94	0	
PANSS negative score	1	9	26/3	9/94	19/8	4/58	-6/6	10/55	0/1	0/794
	2	13	26/6	4/17	20/5	6/72	6/2	8/81	0/027	
PANSS gen psyhc score	1	9	54/2	13/14	42/3	10/46	-11/9	16/19	0/06	0/576
	2	13	54/3	7/60	39/2	14/04	-15/1	12/77	0/001	

The mean changes in PANSS total score have been reduced in both groups, and Group 2 has shown a partially higher reduction than Group 1 in table 3. However, the difference is not significantly different (P=0.954). The PANSS total scores difference in the baseline and the 12th week between the two groups was statistically significant with a P-value of P=0.05 and P=0.002, respectively, which are indicative of the efficacy of the drug in both groups. The mean score changes in the positive subscale were reduced in both groups, and Group 1 showed a slightly higher reduction than Group 2. However, the difference between the two groups was not statistically significant (P=0.693).

The difference in positive subscale scores between the baseline and 12th week in groups 1 and 2 was statistically significant with the P-values 0.027 and 0, respectively. The mean score changes in the negative subscale were reduced in both groups, and Group 1 showed a slightly higher reduction than Group 2. However, the difference between the two groups was not statistically significant (P=0.794). The difference in negative subscale score between the baseline and 12th week in group 2 is statistically significant (P=0.027), however, it is not significant for Group 1 (P=0.1). The mean GPS score changes have been reduced in both groups and in Group 2, the reduction has been slightly higher, however, the difference between the two groups is not significant (P=0.576). The GPS score difference between the baseline and 12th week is significant in Group 2 (P=0.001), while it is not significant in Group 1 (P=0.06).

Table 3: Efficacy ratio per PANSS total score reduction

percentage of PANSS total score reduction	Group 1 (n = ۹)		Group 2 (n = ۱۳)		
	N	%	N	%	P-value
≥ ۲۰%	6	66/7	7	53/8	0/674
≥ ۳۰%	2	22/2	5	38/5	0/648
≥ ۴۰%	1	11/1	5	38/5	0/333
≥ ۵۰%	1	11/1	3	23/1	0/616
≥ ۶۰%	1	11/1	1	7/7	1
≥ ۷۰%	0	0	0	0	0

* The test is not performed on these numbers since the standard deviation is ≥0

The percentage of patients who have at least a 20 and 60% reduction in PANSS total score is higher in Group 1 than in Group 2, while the percentage of patients with at least 30, 40, and 50% reduction in PANSS total score is higher in Group 2 than Group 1, however, this difference between the two groups is not significant.

In Group 1, 66.67% of the patients have shown at least a 20% reduction in PANSS total score, and 11.11% of the patients showed at least a 60% reduction in PANSS total score. In Group 2, 53.84% of the patients have shown at least a 20% reduction in PANSS total score, and 7.7% of the patients showed at least a 60% reduction in PANSS total score.

Discussion:

The results indicate that the two groups were similar in terms of the illness severity, duration of illness, type of diagnosis, marital status, gender, employment status, educational level, and age, in the baseline of the study. Also, the dosage of the drug was the same. The characteristics of the two groups in the baseline emphasize that the two drugs have been evaluated and compared in very similar conditions. In terms of the dropout in patients and the use of anticholinergic drugs in this study, about 35% of the patients who participated in the study dropped out and about 18% of the patients used anticholinergic drugs to control the side effects of risperidone. Some studies on risperidone have shown that the patients' dropout ranges from 14.4 to 80% and the use of anticholinergic drugs to control the side effects of risperidone ranges from 19.05 to 45.45% (9,10).

In Group 1 (Belgian-made risperidone), there were no significant changes in the negative score and gen psych score, however, the positive score and total scores were significantly reduced. In Group 2 (Iranian-made risperidone), the total, gen psych, negative, and positive PANSS scores were all significantly reduced.

In both groups, the PANSS total score was significantly reduced from the baseline to the endline of the study, which is indicative of the efficacy of both drugs, and that there are no differences in terms of the efficacy between the two groups. And it seems that the effects of both drugs are the same. Also, there were no differences between the two groups in terms of the percentage of recovering from illness, and the number of patients with a 20% or above reduction in PANSS score (recovery rate) was 6.7% in Group 1 (Belgian-made risperidone) and 53.8% in Group 2 (Iranian-made risperidone). These numbers have been reported variously in different studies. For example, Gureje et al. reported a 47% recovery in their study (7). And in a study by Chouinard et al., the rate of recovery has been reported to be 73% (11, 12).

In a study conducted by Marder & Meibach, the recovery rate has been 57% (13). Lane et al. also reported a 44% recovery among their patients (14). In all mentioned studies, the recovery rate has been considered to be at least a 20% reduction in PANSS total score and a daily dose of 6mg risperidone.

In another categorization for evaluation of the rate of recovery from the illness by the antipsychotic drugs, a reduction of lesser than 30% in PANSS total score is considered to be a failure in recovery (8). In this regard, 64% of the patients in the current study have not recovered. If a 30-50% reduction in PANSS total score is considered a relative recovery, 18% of the patients will be in this group. If a reduction above 50% in the PANSS total score is considered a full recovery, about 18% of the patients in this study will be in this group. Thus, based on the definition of the rate of recovery, differences in the efficacy of the drugs can be observed which is more or less a numerical range that exists in international studies.

Conclusion

There are no significant differences between the two drugs in terms of statistical and clinical efficacy, and both of them are the same in this regard.

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Conflict of interest
None.
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Ethics Statement
All Permissions to conducting this research has been approved.

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