

COMPARISON OF EFFECT OF OLANZAPINE AND RISPERIDONE ON SERUM PROLACTIN LEVELS IN PATIENTS WITH FIRST EPISODE PSYCHOSIS

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ABSTRACT

Objective: To compare frequency of Hyperprolactinemia with Risperidone and Olanzapine in patients with first episode psychosis.

Study Design: Randomized controlled trial.

Place and Duration of Study: Combined Military Hospital (CMH) Lahore, over a period of six months from Sep 2015 to Feb 2016.

Subjects and Methods: Total 60 patients who had psychosis as accompanying feature in any of the various psychiatric illnesses according to ICD-10 diagnostic criteria were enrolled in this Randomized controlled Trial. Fasting venous blood samples for serum prolactin were collected between 0800 hrs and 1000 hrs at baseline (first visit). The patients were then randomly assigned to receive risperidone or olanzapine by lottery method. Serum prolactin levels were then collected at 3 months follow-up visit. All samples were tested in laboratory of Pathology department, CMH Lahore for measurement of serum prolactin levels and results were verified by a classified pathologist. Confounding variables were identified and excluded by exclusion criteria.

Results: A total of 35 patients (58.33%) developed hyperprolactinemia. The olanzapine group showed 13 out of 30 patients (43.33%) and risperidone group showed 22 out of 30 patients (73.33%) with raised prolactin levels with *p*-value of 0.018 indicating that the difference was statistically significant.

Conclusion: Frequency of hyperprolactinemia is high with risperidone than with olanzapine in first episode psychosis.

Keywords: Antipsychotics, Hyperprolactinemia, Psychosis.

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INTRODUCTION

Psychosis (delusions and/or hallucinations) is a feature of many psychiatric disorders. In psychotic disorders such as Schizophrenia, Acute and transient psychotic episode it is the primary symptom while in mood disorders such as Depression, Bipolar affective disorder it occurs secondary to mood disturbances.

Antipsychotics are the primary drugs used to treat psychosis. These drugs are divided into two classes (Typical and Atypical) based on their tendency to bind Dopamine (D2) receptors.

Typical antipsychotics bind with high affinity while atypical are said to bind with low

affinity. Antipsychotics including atypical are well known to cause Hyperprolactinemia i.e. increased prolactin levels. Drugs having high affinity for Dopamine D2 receptors (Haloperidol) have more tendency to cause hyperprolactinemia¹. Atypical antipsychotics due to their low affinity for Dopamine D2 receptors are less commonly associated but not completely free of hyperprolactinemic effects. Among atypical antipsychotics risperidone and amisulpride affect prolactin levels more frequently while clozapine, olanzapine, quetiapine are prolactin-sparing^{2,3}.

Prolactin is secreted by anterior pituitary gland in a pulsatile manner. Secretion of prolactin is regulated by dopamine, a hormone produced by hypothalamus. Dopamine has inhibitory effect on secretion of prolactin. It acts on D2 receptors present in lactotrophs of anterior pituitary to decrease secretion of prolactin. Antipsychotic

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drugs bind to D2 receptors and block this effect causing increase in prolactin levels⁴.

Hyperprolactinemia in short term causes galactorrhea, amenorrhea in women while raised prolactin levels for prolonged period of time predisposes to osteoporosis and cardiovascular disease. These side effects in turn lead to poor compliance^{5,6}.

A review of the effects of antipsychotic medication on prolactin levels showed that the incidence of hyperprolactinemia was 90% with haloperidol, 80% with pimozide, 62% with risperidone, 31% with olanzapine while clozapine, quetiapine and ziprasidone were prolactin-sparing⁷.

A recent study comparing effects of risperidone and olanzapine on plasma prolactin levels both in short and long term showed that a significantly higher percentage of patients developed hyperprolactinemia in the risperidone treatment group (89%) compared with olanzapine treatment group (45%) at 3 months duration⁸.

The rationale of this study is based on the fact that previous studies have yielded inconsistent results regarding frequency of hyperprolactinemia in patients treated with antipsychotic medication, risperidone and olanzapine⁹. The occurrence of hyper-prolactinemia with these two commonly used antipsychotics (olanzapine and risperidone) needs to be clearly evaluated to help clinicians choose the appropriate drug according to patient's needs.

MATERIAL AND METHODS

The study was randomized controlled trial (RCT) conducted in Combined Military Hospital (CMH), Lahore over a period of six months from 1st Sep 2015 to 29th Feb 2016. Sixty subjects were included in this study through non-probability consecutive sampling. The sample size was calculated by WHO sample size calculator using level of significance 5% and power of test 90%⁸. Ethical approval was obtained from ethical research committee of the hospital and formal

written informed consent was obtained from all the patients included in the study. Patients were equally divided into two groups by lottery method.

Sixty subjects who were enrolled in this RCT were patients of both gender, age ranging between 18-60 years (Mean \pm SD 36.77 \pm 9.686), who had psychosis as accompanying symptom/feature in any of the various psychiatric illnesses according to ICD-10 diagnostic criteria and had normal serum prolactin levels (below 20 μ g/L in males and below 25 μ g/L in females) at the start of study. Criteria that excluded patients from the study included physiological conditions (eg; pregnancy, lactation), medical disorders (e.g. Pituitary tumors, Primary hypothyroidism, Adrenal insufficiency) and concurrent medications (e.g. metoclopramide, methyl dopa, verapamil, dopamine agonists) known to affect serum prolactin levels.

Data Collection Procedure

Demographic data was collected regarding age, gender, occupation, education, marital status. Patients suffering from various psychiatric illnesses were diagnosed by ICD-10 criteria after history and mental state examination by resident/consultant psychiatrist. The patients were randomly assigned to receive risperidone or olanzapine by lottery method. Fasting venous blood samples for serum prolactin were collected between 0800 hrs and 1000 hrs at baseline (first visit) and then at 3 months follow-up visit. Samples were sent to pathology department (CMH Lahore) for measurement of serum prolactin levels and results verified by a classified pathologist. Confounding variables were identified and excluded by exclusion criteria.

Data was analyzed using SPSS 19.0. Descriptive statistics was used to calculate qualitative and quantitative variables. Mean and standard deviation was calculated for quantitative variables (Age). Frequency and percentages were calculated for qualitative variables (Gender, Hyperprolactinemia). Chi-square test/Fisher's exact test was applied to compare the frequency

of Hyperprolactinemia between the two groups. A p -value of <0.05 was considered as significant. Effect modifiers like age, gender, education, occupation, marital status, type of mental illness

the ages of the patients ranged from the youngest being 19 years to the oldest being 58 years (Mean age \pm SD 36.77 ± 9.686). Forty one of subjects [(n=41), 68.3%] were males and nineteen of

Table-I: Baseline patient characteristics.

Patient characteristics	Hyperprolactinemia	Olanzapine Treatment group (n=30)	Risperidone Treatment group (n=30)	Total	p -value
Gender					
Male	Present	10	12	22	0.257
	Absent	12	07	19	
Female	Present	03	10	13	0.04
	Absent	05	01	06	
Age					
18-40 years	Present	11	13	24	0.389
	Absent	09	06	15	
41-60 years	Present	02	09	11	0.008
	Absent	08	02	10	
Marital status					
Single	Present	03	08	11	0.03
	Absent	04	0	04	
Married	Present	10	12	22	0.180
	Absent	12	06	18	
Divorced	Present	-	01	01	-
	Absent	-	01	01	
Widow/widower	Present	0	01	01	1
	Absent	01	01	02	
Occupational status					
Soldiers	Present	03	05	08	0.637
	Absent	05	04	09	
Housewives	Present	01	05	06	0.048
	Absent	04	0	04	
Unemployed	Present	0	06	06	0.083
	Absent	02	01	03	
Retired	Present	0	02	02	0.47
	Absent	02	02	04	
Educational status					
Matriculate	Present	04	05	09	0.37
	Absent	07	03	10	
Uneducated	Present	03	06	09	0.15
	Absent	06	02	08	

were controlled by stratification. For post stratification chi-square test/ Fisher's exact test was used.

RESULTS

Patient baseline characteristics are summarized in table-I. There were sixty patients,

subjects [(n=19), 31.7%] were females. Out of sixty patients fifteen were single [(n=15), 25%], forty were married [(n=40), 66.7%], two were divorced [(n=2), 3.3%] and three were widowed [(n=3), 5%]. The most common occupation seen was of soldiers [(n=17), 28.3%] followed by housewives [(n=10), 16.7%]. These 2 categories

were followed by unemployed [(n=9), 15%] and retired [(n=6), 10%]. Most of the patients were matriculate [(n=19), 31.7%] followed by uneducated [(n=17), 28.3%]. Most frequent diagnosis among patients was Depression with psychotic features [(n=17), 28.3%] followed by Mania with psychotic features [(n=13), 21.7%], Acute and transient psychotic episode [(n=12), 20%], Schizophrenia [(n=11), 18.3%], and Delusional disorder [(n=7), 11.7%].

Out of the total 60 patients, 35 patients (58.33%) developed hyperprolactinemia. The

The difference in hyperprolactinemia between the two treatment groups was significant in older age group i.e. 41-60 years, females and single patients as indicated by their *p*-values shown in table-I (*p*-value <0.05) showing that there is significant effect of risperidone on development of hyperprolactinemia in these groups of patients.

DISCUSSION

Antipsychotics are psychotropic drugs which are used to treat psychosis. Traditionally they are divided into Typical antipsychotics and

Table-II: ICD-10 diagnosis.

ICD-10 Diagnosis	Hyperprolactinemia	Olanzapine Treatment group (n=30)	Risperidone Treatment group (n=30)	Total	<i>p</i> -value
Acute and Transient psychotic episode	Present	02	06	08	0.06
	Absent	04	0	04	
Schizophrenia	Present	01	08	09	0.05
	Absent	02	0	02	
Delusional Disorder	Present	02	02	04	1
	Absent	01	02	03	
Mania with psychotic features	Present	05	03	08	0.23
	Absent	05	0	05	
Depression with psychotic features	Present	03	03	06	1
	Absent	05	06	11	

Table-III: Comparison of hyperprolactinemia in the two treatment groups.

Hyperprolactinemia	Group assigned to patients		Total	<i>p</i> -value
	Group A (Olanzapine)	Group B (Risperidone)		
Present	13	22	35	0.018
Absent	17	08	25	
Total	30	30	60	

Chi-square = 5.554, *p*-value= 0.018 (Significant)

frequency of hyperprolactinemia in olanzapine treated group was 13 out of 30 patients (43.33%) and in risperidone treated group it was 22 out of 30 patients (73.33%). Mean dose of olanzapine and risperidone used was 9.58 mg and 4.5 mg respectively. Chi square test was used to compare the frequency of hyperprolactinemia between the two groups. After the application of the test, the *p*-value was found to be 0.018 (table-III) which showed that the difference in frequency of hyperprolactinemia was statistically significant between the two groups.

Atypical antipsychotics. This classification is based on pharmacological (receptorial) and clinical differences. Typical antipsychotics (eg; Haloperidol) are the drugs which have high affinity for dopamine D2 receptors and have high propensity to cause extrapyramidal side effects and raise prolactin levels. In contrast Atypical antipsychotics (with the exception of risperidone) have less affinity for dopamine D2 receptors and have antagonistic effects at serotonin 5HT receptors. Due to these receptorial differences atypical antipsychotics(olanzapine, quetiapine,

clozapine) can cause metabolic syndrome but have less propensity to cause EPS and are relatively prolactin sparing^{2,3}.

Hyperprolactinemia is an important phenomenon associated with antipsychotic medication and affects quality of life and adherence to treatment. In short term it causes galactorrhea, amenorrhea and decreased libido. Prolactin levels if remain elevated for prolonged period of time predisposes to osteoporosis and cardiovascular disease.

Previous studies have yielded inconsistent results regarding the prolactin sparing effect of atypical antipsychotics⁹. The objective of this study was to compare frequency of hyperprolactinemia with Risperidone and Olanzapine in patients with first episode psychosis. This will help clinicians choose the appropriate drug according to patient's characteristics.

In our study we found out that the frequency of hyperprolactinemia in risperidone treated group was greater than olanzapine treated group and the difference reached statistical significance. This finding is in agreement with previous studies which show that risperidone is more likely to cause hyperprolactinemia than olanzapine^{7,8}. The mechanisms that account for this difference are: (1) greater D2 receptor affinity of risperidone as compared to olanzapine¹⁰ and (2) a higher pituitary versus striatal D2 receptor occupancy for risperidone as compared to olanzapine¹¹.

When patients age was considered the frequency of hyperprolactinemia was greater with risperidone in both age groups A (18-40 years) and B (41-60 years). However the results reach statistical significance in group B showing that there is significant effect of risperidone on development of hyperprolactinemia in age group 41-60 years. Prolactin regulation is a complex phenomenon with part played by various hormones. Estrogens are known to regulate the prolactin cell mass and its lower levels is responsible for the remarkable decrease in serum prolactin concentration after menopause and

possibly explains moderate increase in elderly men due to increased bioavailable estradiol¹².

Gender wise distribution revealed that the frequency of hyperprolactinemia was greater with risperidone in both males and females. In males the results did not reach statistical significance. In females the results were statistically significant showing that there is significant effect of risperidone on development of hyperprolactinemia in females. This is consistent with previous studies which show that women are more prone to develop hyperprolactinemia with antipsychotics than men¹³. This finding can be explained by the fact that estrogen regulates prolactin cell mass as already mentioned¹².

The ICD-10 diagnosis included in our study were Acute and transient psychotic episode, Schizophrenia, Delusional disorder, Mania with psychotic features, Depression with psychotic features. There was difference observed in frequency of hyperprolactinemia between risperidone and olanzapine (greater with risperidone than olanzapine) in all diagnostic groups however the difference was not statistically significant.

Marital status of patients revealed increased frequency of hyperprolactinemia in risperidone group and the results reached statistical significance in patients who were single (unmarried) showing that there is significant effect of risperidone on development of hyperprolactinemia in this patient group.

Considering the occupational status of patients, the difference in frequency of hyperprolactinemia reached statistical significance for housewives. This appears to be result of the greater propensity of females to develop hyperprolactinemia as already explained¹³.

In summary, this study suggests that olanzapine and risperidone differ in terms of occurrence of hyperprolactinemia and the difference reach statistical significance. Female gender and older age are risk factors for development of hyperprolactinemia with risperidone.

CONCLUSION

We concluded that the frequency of hyperprolactinemia is high with risperidone than with olanzapine. Moreover women are more prone to develop hyperprolactinemia with risperidone than with olanzapine.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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