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Original Research Article

A comparative study between first generation and second generation antipsychotics over the development of metabolic syndrome in persons with first episode drug naive schizophrenia

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ABSTRACT

Background: Antipsychotic treatment for schizophrenia is prone for drug side effects. Both typical and atypical antipsychotics are prone for metabolic derangements. The aim of this study was to compare the emergence of metabolic syndrome with haloperidol and risperidone in drug naïve first episode schizophrenics.
Methods: This was a prospective observational study conducted at the Institute of Mental health, Chennai, India from April 1, 2011 to November 15, 2011. 24 patients received haloperidol and 29 patients received risperidone and followed up for 6 months, after obtaining informed consent. PANSS score, AHA criteria for metabolic syndrome, plasma glucose, waist-hip ratio, body mass index and lipid profile were recorded at every two months interval.
Results: PANSS score showed a decrease in both groups, systolic blood pressure showed an increase with Haloperidol and an initial decrease with risperidone while diastolic blood pressure increased with haloperidol. Weight gain, increase in waist circumference and hip circumference, rise in triglyceride levels and fall in HDL cholesterol were equally observed in both groups. Increase in plasma glucose was seen more with risperidone (93.1%). 18.86% (n = 10) developed metabolic syndrome at the end of 6months with no difference in emergence between both groups.
Conclusions: Risperidone may be considered equivalent to haloperidol in efficacy and with minimal changes in metabolic profile. Blood pressure lowering effect of risperidone is more marked in earlier months warranting patient education. Stringent guidelines are needed during antipsychotic treatment to prevent cardiovascular and cerebrovascular morbidity and mortality.

Keywords: Blood pressure, Haloperidol, Metabolic syndrome, Risperidone

INTRODUCTION

Schizophrenia, which has a multifactorial aetiology, probably comprises a group of syndromes, involving genetic, developmental, psycho-neuro-immunological and environmental interactions in manifesting the disease. Psychopharmacology started with the revolutionary introduction of chlorpromazine following which dopaminergic hypothesis of schizophrenia was proposed. These dopamine antagonists like chlorpromazine, haloperidol was the typical or first generation antipsychotics. These drugs were prone to cause tardive dyskinesias along with other side effects, prompting research for drugs with minimal adverse effect

profile and led to the development of dopamine-serotonin antagonists-the atypical or second-generation antipsychotics.[1]

The second generation antipsychotics, like clozapine, even though associated with fewer incidences of dyskinesias, had metabolic derangements like weight gain, hypertension, dyslipidemia and glucose dysregulation which catastrophically increased cardiac and cerebrovascular complications.[2] Weight gain was a liability to both first generation and second generation antipsychotics even when administered for a short period.[3] The pattern of increase was more of subcutaneous and intra-abdominal fat deposition. Additionally, an increase in insulin resistance is anticipated to occur secondary to increase in adiposity.[4] The atypical antipsychotics have a marked propensity for adverse metabolic outcomes, especially dyslipidemia.[5]

The rational of the present study was to find out the emergence of metabolic syndrome with the use of second generation antipsychotics and comparing it with first generation antipsychotics in individuals with drug naive first episode schizophrenia, so as to avoid the disease effect. This will help treating psychiatrists to modify pharmacological treatment and to identify morbid metabolic derangement at the earliest so that corrective measures can be undertaken.

METHODS

This was a prospective observational study conducted at the Institute of Mental Health, Chennai, Tamilnadu, India. Patients who attended the outpatient department from April 1, 2011 to May 15, 2011 with first episode schizophrenia, as per DSM IV-TR criteria, between the age of 18 years and 45 years were included in the study. Patients who had comorbid psychiatric illness, substance abuse, comorbid metabolic diseases (diabetes mellitus, hypertension, obesity, dyslipidemia) or on any drug treatment were excluded from the study. By simple random method, patients were divided into two groups. One group received first generation antipsychotic (haloperidol) and the other group received second generation antipsychotic (risperidone), in doses equivalent to minimum and maximum dose of chlorpromazine. The patients were followed till November 15, 2011 (6months) for the development of metabolic syndrome. During the first visit, complete psychiatric history in socio-demographic data sheet, physical examination, baseline assessment of anthropometric measures and psychopathology were obtained.

To assess psychopathology of the patient, DSM IV-TR diagnostic criteria for schizophrenia, Positive and Negative Symptoms Scale (PANSS) and Simpson Angus rating scale were used.[6,7] To assess for metabolic derangement, American Heart Association (AHA) criteria for metabolic syndrome, Fasting plasma glucose estimation for diabetes mellitus, blood pressure readings (average of 3 recordings taken at 10minutes interval) for hypertension, lipid profile (after 12hours fasting) for dyslipidemia along with waist-hip ratio and body mass index (BMI) were used and these measurements were repeated at two months interval.[8]

Statistical analysis was done using SPSS software version 17. Descriptive data were given in summary statistics. Chi square test was used for categorical variables, Student T-test for unpaired samples for comparison between the two groups, general linear model analysis, multivariate repeated measures and adjustment for multiple comparisons were used to verify the hypothesis that second-generation antipsychotics cause more metabolic derangements than first generation antipsychotics. $p<0.05$ was considered significant.

RESULTS

Around 67 patients were screened for eligibility in to this randomized comparative study. 11 patients were excluded due to substance abuse and co-morbid medical illness. 3 patients were not willing to participate in the study and so the final count was 53. 45.28% (n = 24) were allotted into haloperidol (first generation antipsychotic) group and the remaining 54.71% (n = 29) were allotted into risperidone (second generation antipsychotic) group.

In the present study (n = 53), 62.2% of the patients were females (n = 33). 64.2% of the patients were unmarried (n = 34). 58.6% belonged to the lower socio-economic status (n = 31). 18.9% of patients had positive family history for schizophrenia (n = 10). The drug profile and cumulative doses of both groups were comparable in terms of equivalent doses of chlorpromazine (haloperidol 84mg and risperidone 102mg). There was no significant difference in Simpson Angus score between the two groups (p = 0.638). The comparative data between the two groups are given in Table 1.

During follow up, the PANSS score for the total subjects (n = 53), showed a total reduction of 62.09 at the end of 6 months. The PANSS score reduced by 36.32±2.78 from baseline at the end of two months, 66.25±4.01 at the end of 4months and 62.09±3.89 at the end of 6months. This reduction of score from baseline to every 2month observation was significant (p = 0.00). The PANSS score reduction in haloperidol group was 61.29 while that of risperidone group was 62.99 at the end of 6months. The difference was not statistically significant (p = 0.888).

The rise in systolic blood pressure was statistically significant in haloperidol group from baseline value to the end of 6months (p = 0.004) and this rise was statistically significant than risperidone group (p =0.000). Similarly, the rise in diastolic blood pressure was significant in haloperidol group from baseline value to the end of 6 months (p = 0.005) and this rise was

statistically significant than risperidone group (p = 0.004) (Table 2). In the initial 2months, there was a steep fall of systolic blood pressure in risperidone group, but it stabilized in the subsequent months.

Table 1: Comparison of baseline parameters between haloperidol group and risperidone group of drug naïve schizophrenia patients.

Parameters-Baseline	Haloperidol group (n = 24)	Risperidone group (n = 29)
Mean age (in years)	26.08±6.71	30.48±8.76
Females	66.7% (n = 16/24)	58.6% (n = 17/29)
Marital status-Unmarried	62.5% (n = 15/24)	65.5% (n = 19/29)
Socioeconomic status-Lower	58.3% (n = 14/24)	58.6% (n = 17/29)
Family H/O schizophrenia	16.7% (n = 4/24)	20.6% (n = 6/29)
PANSS score	117.75±30.80	120.55±34.54
Mean weight	54.38±7.91kg	55.62±7.85 kg
Waist circumference	81.69±5.53 cm	83.29±6.55 cm
Hip circumference	91.19±7.11 cm	92.41±5.92 cm
Body Mass Index	21.37±4.07	22.67±3.75
HDL Cholesterol	50.08±4.37 mg%	48.48±4.71 mg%
Triglyceride level	134.12±10.86 mg%	132.45±12.15 mg%
Systolic blood pressure	111.75±12.38 mmHg	110.00±11.70 mmHg
Diastolic blood pressure	71.83±7.88 mmHg	70.71±10.36 mmHg
Fasting plasma glucose	90.92±5.49 mg%	89.83±6.35 mg%
Post prandial plasma glucose	125.75±10.11 mg%	122.69±10.28 mg%

Table 2: Significance of rise in blood pressure in individual groups and in between groups of patients on antipsychotics.

Time interval	Haloperidol Group (n = 24)	Time interval	Risperidone Group (n = 29)	Significance of difference in BP between two groups
Changes in systolic blood pressure				
Baseline	111.75±12.38	Baseline	110.00±11.70	
2 months	116.43±13.67	2 months	102.24±10.92	p = 0.871
4 months	122.27±15.92	4 months	110.31±11.36	p = 0.003
6 months	121.22±10.59	6 months	108.28±11.14	p = 0.000
Significance of rise in BP in group	p = 0.004		p = 0.756	
Changes in diastolic blood pressure				
Baseline	71.83±7.88	Baseline	70.71±10.36	
2 months	74.98±5.19	2 months	71.86±7.26	p = 0.081
4 months	79.36±8.47	4 months	72.21±8.41	p = 0.004
6 months	78.25±7.53	6 months	71.17±9.61	p = 0.004
Significance of rise in BP in group	p = 0.005		p = 0.953	

In the haloperidol group (n = 24), 83.3% (n = 20) patients showed weight gain, while all the patients in Risperidone group (n = 29) developed weight gain. In the total population (n = 53), there was an increase of 1.39±0.17kg at the end of 2months, 1.98±0.29kg at the end of 4months and an increase of 2.59±0.38kg at the end of 6months from the baseline weight. This weight gain was statistically significant (p = 0.000) but there was no significant difference between weight gain in haloperidol and risperidone group (p=0.990). Similarly, even though the Body Mass Index (BMI) showed an overall increase of 0.561±0.07 at the end of 2months, 0.790±0.12 at the end of 4months and 0.968±0.19 at the end of 6months in the entire group (n=53), which was statistically significant (p = 0.000), the difference of rise in BMI between haloperidol group (n=24) and risperidone group (n=29) was not statistically significant (p = 0.499).

There was an increase in hip circumference in the overall population (n = 53), but it was not significant (p = 0.704). The mean increase of hip circumference was 0.39±0.38cm at the end of 2months, 0.66±0.41cm at the end of 4 months and 0.45±0.44cm at the end of 6months from baseline value. Haloperidol group showed an

increase in 87.5% (n=21) while risperidone group showed an increase in all patients (n = 29) but this increase in hip circumference was not statistically significant between the two groups (p = 0.561). Similarly, the mean increase in waist circumference was 0.66±0.47cm at the end of 2months, 0.89±0.46cm at the end of 4months and 0.80±0.54cm at the end of 6 months and the difference between the two groups was not statistically significant (p = 0.246).

In the haloperidol group (n = 24), HDL cholesterol showed a decreasing trend in 79.9% (n = 19) while 89.6% (n = 26) showed a decreasing trend in risperidone group. Even though the fall in HDL cholesterol was seen in the entire group (n = 53), with an observed fall of 3.56±0.75mg% at the end of 2months, 4.53±0.79mg% at the end of 4months and 4.52±0.70mg% at the end of 6 months which was statistically significant (p = 0.000), the difference in the fall of HDL level between haloperidol and risperidone group was not statistically significant (p=0.540). There was a rise in triglyceride levels in the overall group (n = 53) with a rise of 5.45±1.23mg% at the end of 2months (p = 0.000), 8.76±2.27mg% at the end of 4months (p = 0.002) and a rise of 9.87±1.24mg% (p=0.000) at the end of 6months which was statistically significant. Triglyceride levels were increased in 79.1% (n=19) in the haloperidol group and 86.2% in risperidone group (n = 25). The mean difference between the two groups was statistically not significant (p = 0.652).

There was an observed increase in fasting plasma glucose in the overall group (n = 53) with a rise of 3.79±0.99mg% at the end of 2months (p = 0.003), 6.65±1.49mg% at the end of 4months (p = 0.000) and a rise of 6.04±1.03mg% (p = 0.000) at the end of 6months which was statistically significant. This rise in fasting plasma glucose was observed in 87.5% of patients in haloperidol group (n = 21) and 93.1% of patients in risperidone group (n = 27). The mean difference was more in risperidone group and it was statistically significant (p = 0.005).

In the present study, 9.43% (n=5/53) developed metabolic syndrome at the end of 4 months of antipsychotics treatment and 18.86% (n=10/53) patients developed metabolic syndrome at the end of 6months. In the haloperidol group, 8.3% (n=2/24) at the end of 4months and 16.6% (n=4/24) at the end of 6months, developed metabolic syndrome while in the risperidone group, 10.3% (n=3/29) at the end of 4months and 20.6% (n=6/29) at the end of 6months developed metabolic syndrome. This observed difference was not statistically significant.

DISCUSSION

Schizophrenia per se is a risk factor for the development of metabolic syndrome, with a measured two-fold increase in risk, in vulnerable individuals. Treatment with antipsychotics compounds this risk and the liability is more with second generation antipsychotics. Even in the first-generation antipsychotics, there is a differential liability with phenothiazine group drugs like chlorpromazine showing more risk of metabolic syndrome than butyrophenones like haloperidol. In the second-generation antipsychotics, clozapine and olanzapine cause more derangements, risperidone and quetiapine show moderate derangements while ziprazidone and aripiprazole show doubtful liabilities.[9] The present study was one of the few studies done in first episode drug naive schizophrenic individuals which eliminates the risk of disease effect on treatment outcomes.

Among the patients who developed metabolic syndrome (n = 10/53), 7 patients had duration of schizophrenia for less than a year (70%). Positive family history for metabolic derangements was observed in 70% (n = 7/10) while sedentary lifestyle pattern was observed in 80% (n = 8/10). Early response to antipsychotics with more than 40% reduction in PANSS score was positively associated with weight gain, rise in fasting plasma glucose, increase in triglyceride level and decrease in HDL cholesterol which was significant (p = 0.002). This weight gain with antipsychotics in response to reduction of PANSS score was similar to the results obtained by Lane et al.[10] Rise in fasting plasma glucose and triglyceride levels and fall in HDL cholesterol level during treatment with antipsychotics was recorded in the study by Zhang et al.[11] This weight gain and rise in glucose levels was less significant with Risperidone as demonstrated in the study by Chaudhry et al.[12] But in the present study, rise in glucose levels was statistically associated more with Risperidone than haloperidol. The present study did not find any difference in weight gain between risperidone group and haloperidol group but Allison et al in their review found that risperidone induces more weight gain than haloperidol.[3]

Observation of changes in blood pressure showed that the systolic and diastolic blood pressures were raised in the haloperidol group and decreased in risperidone group. The studies by Hempel et al and Choure et al, found that risperidone did not cause significant changes in blood pressure while the present study found a decrease in initial two months followed by regaining normal range.[13,14] This may be due to risperidone significant action at alpha-2 adrenergic receptors. Metabolic syndrome developed in 18.86% of the patients in the present study, with 4 patients in haloperidol group (16.6%) and 6 patients in risperidone group (20.6%). The difference in incidence of metabolic syndrome was statistically not significant. This was in contrast to the results obtained in the study by Kalaimathi et al.[15]

Thus, in the present study, both haloperidol and risperidone caused significant increase in weight, body mass index, plasma glucose, triglycerides, hip circumference, waist circumference and fall in HDL cholesterol. In contrast to other metabolic derangements,

risperidone causes reduction in blood pressure, more so during the initial treatment period, while haloperidol elevated the blood pressure.

Smaller sample size and limited follow up (6months) may have prevented observing changes occurring at a later stage. Dietary pattern and physical activity were not observed which can mask drug efficacy.

CONCLUSION

To conclude, in the absence of significant difference between the two groups, among the second-generation antipsychotics, Risperidone may be considered equivalent to Haloperidol in efficacy and minimal changes in metabolic profile. The blood pressure lowering effect of Risperidone is more marked in the earlier months of treatment and this warrants adequate patient and caregiver education. This also warrants stringent guidelines to antipsychotic treatment to prevent cardiovascular and cerebrovascular morbidity and mortality.

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