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A COMPARATIVE STUDY BETWEEN FIRST GENERATION AND SECOND-GENERATION ANTIPSYCHOTICS OVER THE DEVELOPMENT OF METABOLIC SYNDROME IN SCHIZOPHRENIA PATIENTS

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ABSTRACT

Introduction: Metabolic syndrome denotes a constellation glycemic dysregulation, hypertension, dyslipidemia, elevated body mass index producing hypercoagulable and proinflammatory state. Antipsychotics especially, second generation drugs cause more derangements. It occurs in schizophrenia which itself is a vulnerable factor. Hence aim of our study is to compare the development of metabolic syndrome between these groups in drug naive first episode schizophrenia. **Method:** This is a randomized, prospective study. Risperidone had 29 and haloperidol 24 persons. They were assessed at baseline, second, fourth and six months. **Result:** Significant changes occurred in elevation of body mass index, serum triglycerides, plasma glucose, and HDL cholesterol. This correlated with reduction in PANSS score, more so in the first two months, without significant inter group differences statistically. The risperidone group caused significant reduction in both systolic and diastolic blood pressure as against gradual rise in haloperidol group, more marked in first two months. **Discussion:** In our study over all 18.86% developed metabolic syndrome according to American heart association criteria, 20.6% in risperidone and 16.6% in haloperidol without significance statistically. This pattern of moderate potential of risperidone among second generation antipsychotics and the relatively low incidence of high potent haloperidol were shown in various studies. Risperidone's reduction reveals the therapeutic implication of stringent precaution on initiation of therapy. These inferences may be replicated in future with more samples and longer duration

KEYWORDS : Metabolic syndrome, antipsychotics

INTRODUCTION

Schizophrenia is a variable, significant and disruptive psychopathology, affecting every aspect of human life experiences like perception, cognition, emotion and behavior, resulting in profound and often long-lasting impairment, not only for persons affected, but also for the family and society, causing huge consumption of health costs, distress, loss of manpower, quality of life and productivity and 'arguably the worst disease affecting mankind, even AIDS not exempted'[1].

It has puzzled physicians, philosophers and general public alike for centuries, as if it is a single disease, but it is probably comprising a group of syndromes due to multifactorial etiology involving genetic, developmental, psychoneuro immunological and environmental interactions in manifesting the disease.

Schizophrenia affects approximately 1% of the population, involving all cultures, society, race and nations, and commonly affecting during the fertile period of adolescent and young adulthood with a tendency for chronic course.[2] The treatment of schizophrenia has evolved over a long period of history with ancient remedies of plant extracts, with the revolutionary introduction of chlorpromazine in the 1950's and the beginning of research on psychopharmacology[3]. Based on the clinical improvement of psychotic symptoms and molecular studies of neurotransmitters and receptors, the dopaminergic hypothesis of schizophrenia was proposed for this early introduction of psychotropic drugs, following the introduction of chlorpromazine, preferentially blocking dopamine 2 receptors, hence these drugs were called dopamine antagonists or typical or first generations antipsychotics.

Apart from the effectiveness, it caused movement disorders of both acute and chronic in addition to other side effects, prompting research for drugs with minimum side effect profile resulting in the introduction of Dopamine-serotonin antagonists or atypical or second-generation antipsychotics with different side effect profiles and equal efficacy except clozapine with much enthusiasm.[4]

Although they were associated with less incidence of dyskinesias, soon it was found that they cause various derangements in metabolic parameters like weight gain, hypertension, dyslipidemia and dysregulation of glucose metabolism, which are established risk factors for cardiac and cerebrovascular complications, which causes catastrophic implications and premature death, requiring long term prophylaxis, dispelling the myth of superiority of atypical over the typical antipsychotics.

So, the rational of the study is to find out the emergence of metabolic syndrome, which was established in various studies in the past, of the second-generation antipsychotics and comparing it against first generation antipsychotics, in individuals with schizophrenia.

METHODOLOGY:

This study is done as prospective comparative randomized 6 months duration, at a tertiary care medical college. Apart from history, both patient and informants were explained about the details of the study and the informed consent was obtained both from the patient and the informants in the prescribed format. The institutional ethical committee's approval was obtained prior to the study and the protocols were followed throughout the study. Cases were selected from outpatient department of department of psychiatry. Patients who had first episode schizophrenia as per DSM IV-TR, aged 18 to 45 years of both sexes were included in the study. Patient who had comorbid psychiatric illness., substance abuse., diabetes mellitus, hypertension, obesity, dyslipidemia and other medical illness were excluded, the total number of individuals selected is 50. They were divided in to two groups with 24 in haloperidol and 26 in the risperidone by simple random method. Any one drug in first generation or second-generation group of antipsychotics was used with Chlorpromazine equivalent doses of minimum and maximum dose. Anticholinergic and benzodiazepines were used if needed. Drugs were allotted by simple random method by the treating clinician.

DSM IV-TR -Diagnostic criteria for schizophrenia. PANSS [Positive and negative symptoms scale]. Simpson Angus rating scale were used. Metabolic assessment was done as per AMERICAN HEART ASSOCIATION criteria for metabolic syndrome. Every two months-Laboratory investigations in additions to anthropometric measurements. Statistical analysis: Done using IBM SPSS statistics version 22.0. Tests used were Students T test. Chi-square test.

RESULTS

The current study is a randomized, prospective, comparative one between risperidone and haloperidol. The samples were first episode drug naïve schizophrenia, divided into two groups by simple random method. Risperidone group had 26 patients and 24 patients in haloperidol. The mean age in risperidone was 36.48 and 29.32. The majority were female, 66.7% in haloperidol group and 58.6% in Risperidone group. The majority of the people were unmarried (64.2%) as against married one. It is 62.5% in haloperidol group and 65.5% in risperidone group. Socioeconomic status was classified into lower, middle and upper and majority were lower class (58.6%).

Most of the persons were sedentary (66%) without significant inter group differences. In our study 18.9% of samples had positive family history. Simpson angus score-no significant group difference (p value - 0.638).

Drug profile of both groups were as follows and there is no much difference between both groups after calculating chlorpromazine equivalent doses in terms of mg of cumulative risperidone (risperidone 102mg and for haloperidol group 84mg). Illness duration was classified into less than one year and more than one year. After applying chi square test no significant variation was found between

both groups.

At the end of two months the dependent variables were assessed. Increases in weight, triglycerides, HDL cholesterol, fasting blood sugar, body mass index were more prominent with highly significant p value (p value -0.002 for HDL, p value - 0.018 for PANSS reduction, p value -0 .001 for weight, triglycerides, blood sugar).

There was a significant difference was found in blood pressure of both systolic and diastolic with highly significant p value of .001, which is not found in another parameters. The mean fall is 3.2 systolic and 2.6 in diastolic for risperidone, and mean rise of 4 in systolic and 2.1 in diastolic for haloperidol. The same pattern of significant difference as in two months was continued in blood pressure changes between risperidone (p value -0.004) and haloperidol (p value - 0.003). At the end of six months the inter group differences were more marked with p value of .000 for systolic and p value of .004 in risperidone and .005 in haloperidol.

Reduction in PANSS score is significant from baseline to second months and from second month to fourth month. (p value - 0.018). The group difference is insignificant. (p value - 0.888). Rapid fall in PANSS occurred almost 40 points reduction in first two months.

Weight gain is more marked in the first two months with a mean of 1.394 kg and less rise between 2 to 4 months. Tests of Between-Subjects Effects show less significant (p value -0.990) Significant change occurred as in weight gain with p value of .001 during the first two months. BMI-as in weight the most vulnerable period is first two months- p value -0.001

HDL cholesterol changes occurred in 19 persons (79%) in haloperidol group and in 24 persons (92%) in risperidone group. There are no differences between the groups (p value -0.540). HDL decrease during the early period is highly significant (p value -0.002). The HDL changes is less from 4th month to 6th month (p value - 0.858).

Hip circumference change seen 21 persons (87.5%) in haloperidol group and in all persons in risperidone group, it is more marked from 2nd month to 4th month (p value - 0.001) without group differences. Hip circumference rise is more up to 4 months (p .000) without inter group difference.

Increased triglyceride differences were seen in 19 persons (79%) and 25 persons (96%) in risperidone group, which is highly significant during the first two months (p value -0 .012). As seen in the graph 6-point rise seen in first 2 months (p value -0.001) and less rise from 4th to 6th month.

Blood sugar rise is more in the first two months with p value of .000 and .003 fasting sugar value rose up to 7 points in the first 4 months with p value of .000 waist circumference increases in waist circumferences were seen in 21 persons (87.5%) in haloperidol group and 23 persons (88%) in risperidone group with the p value of 0.005. This is more marked during the first two months as seen in the graph.

Overall in our study over all 20% developed metabolic syndrome according to American heart association criteria, 23% in risperidone and 16.6% in haloperidol without significance statistically.

DISCUSSION

Schizophrenia itself is a vulnerable one with at least two-fold increased risk factor for the development of metabolic syndrome. Treatment with antipsychotics unequivocally is associated with differential liabilities by various drugs belonging to both first generation and second-generation groups. Among the first generation, the phenothiazine group like chlorpromazine has more risk than high potency butyrophenones like haloperidol. After the introduction of second-generation antipsychotics, it was found that they cause more metabolic derangements than first generation antipsychotics by various studies. Clozapine and olanzapine causes more derangements, risperidone and quitiapine to the moderate extent.ziprazidone, aripiprazole has doubtful liabilities. The current study is one of few studies done in first episode drug naive persons to eliminate the disease effect and very few studies were done in these populations.

At the end of two months in metabolic derangements, there are no differences among educational status, marietal states, religion, and occupation. Out of 10 persons who developed metabolic syndrome, 7 persons had illness duration less than 1 year. sedentary lifestyle pattern was seen in 8 persons and positive family history of metabolic diseases in 7 persons. Early response to anti psychotics with more than 40% reduction as seen in PANSS score, was positively associated with weight gain, rise in fasting plasma glucose, increases in triglycerides, decreases in HDL cholesterol significantly. This pattern was reported earlier by Lane et al[5]. The correlation of glucose regulation with rise in body mass index may be secondary to adiposity. -Eder et al[6]. This may contribute to 30 to 40% of variance of insulin resistance -Farin et al[7]. At the same time a significant population develop insulin resistance independent of it-Koller et al[8]. Risperidone had minimal propensity to increase waist circumference rather than hip circumference without significant difference between the groups in overall increases in body mass index. In both systolic and diastolic blood pressure, there was reduction in risperidone group(mean score 9.37) with high significant p value of .001 as against rise in haloperidol group(mean rise 7). This may be explained by the risperidone's significant action at alpha-2 adrenergic receptors. No persons met the criteria for metabolic syndrome during the first two months. All other parameters of metabolic components correlated with the later development of metabolic syndrome as shown in earlier studies.

At the end of four months, the differences in blood pressure change is significant (p.001) between the groups with rise in both groups 7.14 in risperidone and 2 in haloperidol and the overall change is insignificant. Two persons in haloperidol (8.3%) and 3 persons (10.3%) in risperidone group developed metabolic syndrome. At the end of six months 10 persons (20%) developed metabolic syndrome as per the US national cholesterol education treatment programme. Haloperidol group caused 4 persons (16.6%) and risperidone group caused 6 persons (23%) with minimal increases in the risperidone group, which was found to be statistically insignificant. The minimal difference in producing metabolic changes between risperidone and haloperidol was shown in various studies like one conducted by Saddichsa, Manchunatha et al [9], a short term prospective study (6 weeks duration).The changes in blood glucose level occurred in 9.1% in risperidone and 9.7% in haloperidol group. This study was conducted in Indian population. A similar Indian study done by Shiv Gautham,Parth singh Meena in drug naive schizophrenia, which is a randomized prospective study done for 4 months showed 11.66% metabolic syndrome after 4 months[10]. No patient met criteria for metabolic syndrome with haloperidol, with minimal changes and 10% in the risperidone group developed metabolic syndrome. A similar study by Bishop et al in schizophrenia showed weight gain in 30.6% for risperidone and 22.4% for haloperidol[11].

CONCLUSION

Antipsychotic drug both risperidone and haloperidol causes significant rise in weight, body mass index, plasma glucose, triglycerides, HDL cholesterol, hip circumference, waist circumference. Risperidone has slight preference to elevate waist circumference rather than hip circumference compared with haloperidol. This shows the need for stringent guide lines in antipsychotic treatment to prevent the cardiovascular and cerebrovascular morbidity and mortality.

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