Research Report

INCIDENCE OF METABOLIC SYNDROME IN PATIENTS TREATED WITH CLOZAPINE IN A TERTIARY CARE CENTER IN CENTRAL KERALA

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Submitted on: 10/8/2019 Published online: 1/12/2019

ABSTRACT

Background: Clozapine is widely used for the treatment of resistant Schizophrenia (Sz). Metabolic syndrome (MetS) is its recognized side effect. Reports on the side effects of Clozapine are scanty from Kerala. Hence a prospective observational study was conducted.

Aim: The aim of the present study was to find the incidence of Metabolic syndrome in patients with psychosis, after 12 weeks of treatment with clozapine in a tertiary care centre in Kerala.

Methods: Patients diagnosed as Schizophrenia or Delusional disorder based on International Classification of Diseases (ICD)-10 and not meeting the threshold criteria for MetS according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), and on Clozapine treatment were recruited and followed up for at least 12 weeks. Augmentation, when needed, was limited to Amisulpride, Aripiprazole, and/or Modified Electroconvulsive Therapy (MECT). Bodyweight, waist circumference, blood pressure, fasting blood sugar, and triglycerides levels were measured at the enrolment and after 12 weeks. Seventy-five patients completing follow up for 12 weeks were considered as study subjects. Patients who fulfilled NCEP ATP III criteria at 12 weeks were diagnosed as having MetS.

Results: Study sample of 75 had not met the threshold criteria of NCEP ATP III based MetS diagnosis at the study entry. But among them, 23 met no criteria, 23 met one criterion and 29 met two criteria. Out of 75 patients, 32 (42.7%) developed Metabolic Syndrome at three months. Among 23 who met no criteria at intake, 3 (13%) developed MetS, while it was 9 (39%) in 23 who met 1 criterion and 20 (69%) in 29 who met 2 criteria.

The mean Clozapine dose at discharge was 514±148 mg in those who developed MetS while it was 428±164 mg in those who did not. This difference was statistically significant ($p<0.05$).

Conclusion: Incidence of MetS is high in Clozapine receiving Psychotic patients. The present study showed that in the study population, risk factors have a cumulative effect on the development of this side effect, and the risk is high when the dose of clozapine is higher.

Keywords: Clozapine, side effects, metabolic syndrome, dose relationship

Peter K J, Praveenlal K, Saibunnisa K B. Incidence of Metabolic Syndrome in patients treated with Clozapine in a tertiary care center in central Kerala. Kerala Journal of Psychiatry 2019;32(1):32-38. doi: 10.30834/KJP.32.1.2019.169

INTRODUCTION

Clozapine is a second generation antipsychotic widely used for the treatment of Schizophrenia (Sz), indicated explicitly for resistant cases.[1,2] Metabolic syndrome (MetS) is one of its recognized side effects.[3] The MetS is a common metabolic disorder characterised mainly by obesity.[4] Commonly used criteria for the diagnosis of MetS are National Cholesterol Education Plan Adult Treatment Plan (NCEP ATP III) and International Diabetes Foundation definition (IDF). The former is not based on any hypothesized mechanism and hence has wider acceptance.[5] Abnormal glucose metabolism in Sz was reported in pre-antipsychotic era also.[6,7,8] Freyberg observed reports of a higher prevalence of diabetes in schizophrenic patients compared to the general population.[8] Among second generation antipsychotics, Clozapine and Olanzapine produce abnormalities in metabolic parameters most frequently.[9,10]

Though Clozapine is widely used in Kerala by practising psychiatrists, reports on its side effects are scanty, and no report was found on the incidence of metabolic syndrome among the users. Hence this prospective observational study was undertaken.

METHODS

The study was conducted in a tertiary care hospital attached to a Missionary run Medical College in central Kerala. The proposal was approved by the Institutional Review Board. Cases were screened from the Outpatient (OP) clinic of the Psychiatry department and admitted to ward for starting Clozapine. All cases receiving clozapine admitted consecutively were enrolled for the study based on inclusion and exclusion criteria.

Patients diagnosed as Sz (not limited to resistant cases) or Delusional disorder (Dd) according to International Classification of Diseases (ICD)-10 with no MetS according to NCEP ATP III criteria (Appendix) [11,12] were enrolled for the study and followed up for 12 weeks. NCEP ATP III definition is easy to apply for clinical and epidemiological use.[5] Written informed consent obtained from all participants or relatives.

Patients with age below 18 years and above 60 years, clinically suspected organic brain syndrome, or other serious physical illnesses were excluded from the study.

Subjects were recruited for over two years, from 2015 to 2017, in the study centre. Metabolic and anthropometric measurements such as weight, height, waist, and hip circumference, systolic and diastolic blood pressure, fasting blood glucose and fasting lipid profile were taken. All these measurements were done at the time of enrolment into the study and repeated after 12 weeks. Those who fulfilled NCEP ATP III criteria at the end of 12 weeks were diagnosed as MetS. Baseline Electrocardiography (ECG), daily monitoring of symptoms, pulse rate and blood pressure, weekly monitoring of total and differential blood count, were done as part of routine clinical care while building up the required dose for optimum therapeutic response.

Statistical analysis

IBM Statistical Package for Social Sciences (SPSS) Version 20 was used for analysis. Numerical variables expressed as mean and standard deviation and categorical variables expressed as frequency and percentages. To test the statistical significance of the difference in mean values of study variables

Table1: Baseline NCEP ATP III status

Criteria	Status	Frequency	Percentage
TG >150mg/dl or on treatment	Met	8	10.7
	Not met	69	89.3
Waist Circumference>40inches(M) >35inches(F)	Met	18	24
	Not met	57	76
Fasting glucose >110mg or on treatment	Met	3	4
	Not met	72	96
HDL Cholesterol <40mg/dl(M)<50mg/dl(F) or on treatment	Met	38	50.7
	Not met	37	49.3
Systolic BP >/=130mms Hg	Met	13	17.3
	Not met	62	82.7
Diastolic BP >/=85mms Hg	Met	7	9.3
	Not met	68	90.7

TG- Triglyceride, HDL- High-Density Lipoprotein, BP – Blood Pressure, M- Male, F- Female

with and without MetS, independent sample t-test was used. The paired t-test was applied to compare the mean values of body weight from baseline to 12 weeks follow up.

RESULTS:

The present study was a prospective observational study to assess the incidence of MetS developing over 12 weeks in patients treated in the psychiatric department of a tertiary care centre, Thrissur, Kerala.

Among the 75 patients, there was a male preponderance with 47 males (62.7%) and 28 females (32.8%). At the study intake, their mean age was 28.57(SD 8.71) years, and mean body weight was 61.99 (SD=13.21) Kgs, 59 (78.7%) patients were diagnosed as Schizophrenia and 16(21.3%) were diagnosed as Delusional Disorder. The NCEP ATP III status of patients at the study entry is given in Table1. At the exit from the study, the mean body weight increased to 65.43(SD=13.60) Kgs. The increase was statistically significant at <0.001(t=16.128). Of the total 75, 32(42.7%) patients developed MetS at the time of follow up at three months.

The conversion to Mets varied between subgroups based on the presence of the number of factors in the criteria for NCEP ATP III. Among those 75 cases studied, 29 fulfilled two criteria, 23 met one criterion, and the remaining 23 fulfilled no criteria at the time of recruitment. The rates of conversion to full criteria for MetS in these three categories are given in Table.2.

Table 2: Cumulative presence of NCEP ATP III criteria and conversion rate to metabolic syndrome.

Meeting criteria	Status at intake	Status at exit	Conversion percentage
None	23	03	13.04
One	23	09	39.13
Two	29	20	68.97
Total	75	32	42.67

Table 3: Status of parameters of metabolic syndrome at onset and post-treatment

Criteria	Number with Pre-treatment absence	Number with post-treatment presence	Conversion percentage
Waist circumference	57	13	22.81
Fasting glucose	72	19	26.39
Triglyceride	69	20	29.98
HDL Cholesterol	37	11	29.73
Hypertension (Systolic, Diastolic or both)	62	32	51.61

Out of 75 patients, when waist circumference was compared, 57 patients did not fulfil the criteria at the beginning of the treatment. Among them, 13 converted to fulfilling criteria. Of the 72 patients who did not meet criteria for fasting glucose at the onset of the treatment, 19 turned to meet the criteria. Of the 69 patients that did not meet criteria for triglyceride levels onset of treatment, 20 patients converted to meeting the criteria. Similarly, 37 patients who did not meet criteria for HDL cholesterol initially, 11 patients converted to meeting criteria. Finally, when hypertension levels were compared, among the 62 patients who did not meet the criteria, 32 patients turned to meet the criteria. The conversion rate of each sub-criteria of NCEP ATP III is given in Table 3.

Table 4: Dose of Clozapine and the presence of metabolic syndrome at discharge.

Metabolic syndrome	N	Clozapine dose at discharge		P-value
		Mean	SD	
Present	32	514.06	147.68	0.022 (t=2.35)
Absent	43	427.91	164.13	

The mean Clozapine dose at discharge in the group who developed MetS was higher than those in the group without the syndrome. The difference of dose was 86 mg per day which was statistically significant (Table. 4)

DISCUSSION:

The effectiveness of clozapine in the treatment of refractory schizophrenia has been universally accepted. The need for optimization of clozapine use and properly informing practitioners were highlighted by Stephanie Warnez and Silvia Alessi-Severini.[2] Persons with severe mental illnesses have increased risk for metabolic disorders characterized by obesity, type 2 diabetes mellitus, dyslipidemia, and hypertension.[13]

A prospective study on 120 Sz patients conducted at Jaipur, showed Second-generation antipsychotics causing significantly more changes in the metabolic parameters, increasing the chances of developing metabolic syndrome and associated disorders like diabetes mellitus type-II and cerebrovascular accidents, in comparison to 30 patients on conventional antipsychotics.[3] Our incidence 43% matched the figures of 47% reported by Grover *et al.* from Chandigarh. Their sample also had predominance for males (62.7%) though the mean age was higher (35.7yrs). The above-mentioned study also had used NCEP ATP III citeria.[1]

More the number of criteria of NCEP ATP III higher was the incidence of MetS. The presence of risk factors at intake appears to have a cumulative effect on the development of MetS in psychotic patients at 12 weeks after taking Clozapine. Studying individual components of criteria was not an objective of our study, and data on individual items were too small to make any valuable explanation. Among the four components, hypertension was observed to be in higher frequency, which suggests further exploration of the action of clozapine on hypertension.

The study of Antonio Ventriglio et al. which has reported a higher risk of MetS for Quetiapine and Olanzapine in comparison with risperidone, haloperidol, or aripiprazole, have shown a dose-related incidence of MetS.[14] The latter observation is in agreement with our findings.

A Cochrane review of 27 studies on the efficacy of Clozapine compared to other Second-Generation Antipsychotics confirms that it is more efficacious than zotepine and risperidone, but limitations are side effects such as hypersalivation, sedation, and seizures. Weight gain and leucopenia are also mentioned.[9]

Pre-diabetes and metabolic abnormalities among Sz patients on clozapine and olanzapine need to be identified and treated because of high prevalence.[15] Cardiovascular and metabolic risk factors associated with Clozapine treatment are frequently under-treated. Emotional instability and complex treatments contribute to increased risk of metabolic disorders.[11] Minimisation of Polypharmacy, smoking cessation and lifestyle interventions are recommended in the high-risk population.[16] Insulin resistance, visceral adiposity, atherogenic dyslipidemia, and endothelial dysfunction are the core features of MetS, and they are interrelated, having common mediators, pathways and pathophysiological mechanisms.[5] Chronic inflammation is proposed to be associated with visceral obesity, insulin resistance and MetS perse.[4] Links between signalling pathways associated with schizophrenia and metabolic syndrome are suggested, hypothesising pathophysiologically direct relation between genesis of schizophrenia and metabolic control.[8] But it had been shown that weight reduction response to pharmacologic treatment for clozapine-induced MetS in Sz did not show worsening of psychopathology, thereby pointing to the indirect relationship.[17]

It is reported that atherogenicity and endothelial dysfunction are crucial than isolated hypertension or hyper-lipidemia.[5] But our results showed that each factor is important as they have a cumulative influence on the development of MetS.

Clozapine induced MetS need lifestyle modification as the initial intervention of choice. Pharmacological treatment is indicated if lifestyle modification alone fails.[4]

Limitations

Ours is a hospital-based study and hence cannot be generalized to patients living with psychosis in the community. The same is with the sample size as it is small; therefore, it cannot be generalized. Incidence after 12 weeks of treatment was only considered. A longer time period is required for calculating actual incidence, mainly because those on treatment are likely to continue it long term. Socio-demographic factors, lifestyle pattern and other factors that contribute to MetS were not considered in this study. The co-

morbidities were not studied, which is another limitation. The serum level of Clozapine was not measured, and hence it can't be decided about the relationship between syndrome and bioavailable Clozapine.

Conclusion

The incidence of metabolic syndrome was high in the Clozapine receiving psychotic patients. Pre-treatment existence of any component of NCEP ATP III criteria appeared to have a cumulative effect on the development of this side effect and risk was higher when a higher dose was used.

Acknowledgements

Authors would like to thank Dr Unnikrishnan (biostatistician) for his support during the course of this research.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix

NCEP ATP III Definition of Metabolic Syndrome

Criteria	Metabolic syndrome is present if three or more of the following five criteria are met: 1. waist circumference over 40 inches (men) or 35 inches (women). 2. blood pressure over 130/85 mmHg. 3. fasting triglyceride (TG) level over 150 mg/dl. 4. fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women). 5. fasting blood sugar over 110 mg/dl.