

EFFECT OF METFORMIN IN REDUCTION OF ANTI-PSYCHOTIC MEDICATION INDUCED WEIGHT GAIN IN SCHIZOPHRENIA

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Date Received:

January 15, 2020

Date Revised:

February 17, 2020

Date Accepted:

February 20, 2020

ABSTRACT

Objective: To determine the effect of Metformin in reducing Olanzapine induced weight gain in people with Schizophrenia.

Methodology: This randomized controlled trial was conducted on 138 patients at Psychiatry unit, Lady Reading Hospital Peshawar, from August 2016 to February 2017. Patients diagnosed with schizophrenia by consultant psychiatrists in both outpatient and inpatient were included. They were randomly allocated to two groups by lottery method. Intervention group received Olanzapine plus Metformin while control group received Olanzapine plus placebo. Weight was measured in kilograms in all patients at baseline and follow-up at 12 weeks.

Results: Number of patients included were 138 (69 in each group) with age range of 17 to 60 years. Mean age of participants for group A was 29 years with SD \pm 2.68 while for group B it was 30 years with SD \pm 2.91. Group A had 60% male and 40% female patients whereas in group B, 62% patients were male and 38% patients were female. In group A mean decrease in weight was 2.62 kg (SD \pm 3.13) while in Group B mean decrease was 1.57 Kg (SD \pm 2.83).

Conclusion: Mean decrease in weight from baseline in Olanzapine plus Metformin group was more than the Olanzapine plus placebo group.

Key Words: Metformin, Olanzapine-induced weight gain, Schizophrenia

This article may be cited as: Khan MF, Haq SU, Murad K, Nazar Z. Effect of metformin in reduction of anti-psychotic induced weight gain in schizophrenia. *J Postgrad Med Inst* 2020; 34(1): 41-4.

INTRODUCTION

Schizophrenia is a severe mental condition which is usually chronic and of continuing course. Schizophrenia can be better explained in four peculiar phases i.e. the premorbid, prodromal, deterioration, and chronic or residual phase. Mostly people diagnosed with schizophrenia recover if treated appropriately in their initial stage. But usually these patients present late and repeated episodes with inadequate management or non-compliance leads to other significant neurological complications¹. According to existing evidence, weight gain and metabolic alterations are clinically significant side effects of atypical antipsychotic medication which are noticeable usually after 10 weeks of treatment². Olanzapine is associated with significant increase in body weight and causes 0.9 kg of weight gain from first month up to 6-10 kg body weight gain after one year of treatment³. The basic and primary mechanism for olanzapine induced body weight gain is the hunger stimulation and insulin resistance⁴.

Among people with schizophrenia, 30% of the patients treated with Olanzapine gained 7% of their body weight from their baseline assessments as reported in

the study of clinical antipsychotic trial of intervention effectiveness (CATIE)⁴. Another study found that using Olanzapine and Clozapine compared to other atypical antipsychotics led to noticeable body weight gain⁵.

Effective and productive pharmacological and non-pharmacological approaches are intensively required for controlling weight gain during Olanzapine treatment⁶. It has been reported that many other medications such as Amantadine, Nizatidine, Ranitidine, Famotidine, Topiramate, Fenfluramine, Reboxetine, Fluoxetine, Fluvoxamine, Sibutramine, Dextroamphetamine, d-Fenfluramine, Orlistat, Phenylpropanolamine, Rosiglitazone and Metformin are effective in prevention of antipsychotic-induced weight gain^{7,8,9}. In the United States, Metformin and Topiramate are mostly used for this purpose¹⁰.

It has been shown in the light of previous research that Metformin (anti diabetic agent), is exceptionally effective because of its dual mechanism of reducing body weight and improving insulin sensitivity. Metformin has been reported to improve glycemic control and promotes significant weight loss in both diabetic and non-diabetic subjects^{11,12}.

Now a days weight gain is a vital concern in people receiving atypical antipsychotics for schizophrenia apart from other issues of metabolic syndrome. In addition to ill effects of schizophrenia itself, the patients develop other mental and behavioral complications related to weight gain in the course of their treatment with Olanzapine. The aim of this study was to generate local statistics about the effect of Metformin compared to placebo in reducing the weight gain in people receiving Olanzapine for management of schizophrenia.

HYPOTHESIS:

Metformin has beneficial effect on preventing olanzapine induced weight gain in people with schizophrenia.

METHODOLOGY

This randomized controlled trial was conducted at Psychiatry unit, Lady Reading Hospital Peshawar from August 2016 to February 2017. Sample size was calculated by using the mean weight loss in the Olanzapine plus Metformin group as 2.8 - 3.2 kg compared to 1.4 - 2.6 kg in the Olanzapine plus placebo group, keeping 95% confidence interval and 80% power of the test. it was 69 patients per group. Consecutive non probability sampling technique was used for enrollment of patients.

Diagnosis of schizophrenia was based on ICD-10 criteria by consultant psychiatrist. Inclusion criteria maintained that patients should have been receiving Olanzapine monotherapy for at least 3 months. Patients with normal physical examination, normal baseline investigations (Full blood count, Urea, Blood glucose and SGPT) and electrocardiogram (ECG) were included in the study. Patients with following characteristics were excluded from the trial i.e. Pregnant or lactating women, patients on hormone replacement therapy, mental retardation, medical conditions such as Diabetes Mellitus, dyslipid-

emia, cardiovascular diseases, and hypertension. People with severe drug dependence requiring inpatient treatment and/or detoxification were also excluded. Patients were randomly allocated into two groups by lottery method. Group A was Olanzapine plus Metformin group (Intervention group) which received standard doses of Olanzapine (5-20 mg) and Metformin (500mg twice a day) while group B was Olanzapine plus placebo (control group) which received standard doses of Olanzapine (5-20 mg) and placebo (1 tab twice a day). After obtaining informed consent and keeping confidentiality, initial demographic data was collected and baseline weight in kilogram was measured for all patients. All the assessors were kept blind of the patients' allocation. Analyses were performed using the Statistical Package for Social Sciences (SPSS), version 20.00. Focus of the data analysis was on the basis of Intention to treat. P values were calculated for statistical significance between means of the two groups of patients.

RESULTS

A total of 138 patients were recruited in this trial (69 each group). In group A, 41 (60%) patients were male and 28 (40%) patients were female whereas in group B, 43 (62%) patients were male and 26 (38%) patients were female. (Table no 1). Mean dose of Olanzapine was 14.2 mg in intervention group while it was 12.8 in control group.

In group A mean baseline weight was 68 kg with SD \pm 7.71 while mean weight at follow up was 65.38 kg with SD \pm 4.58 and the mean decrease in weight was 2.62 kg with SD \pm 3.13. In group B, mean baseline weight was 70 kg with SD \pm 8.68 while mean weight at follow up was 68.43 kg with SD \pm 5.85 and the mean decrease in weight was 1.57 kg with SD \pm 2.83. (Table no 2).

Table 1: Gender Distribution (n=138)

GENDER	GROUP A	GROUP B
Male	41(60%)	43(62%)
Female	28(40%)	26(38%)
Total	69(100%)	69(100%)
Mean and SD	29 year \pm 2.68	30 year \pm 2.91

Table 2: Weight Distribution (n=138)

WEIGHT	GROUP A (n=69) Mean and SD	GROUP B (n=69) Mean and SD	*P value
Base line	68+ 7.71	70Kg + 8.68	0.1547
Follow up	65.38+ 4.58	68.43+ 5.85	0.0009
Decrease	2.62 kg + 3.13	1.57 kg + 2.83	0.0406

DISCUSSION

Atypical antipsychotics especially Olanzapine has significant side effects on metabolic profile and body weight^{2,3}. The clinical antipsychotic trials of intervention effectiveness (CATIE) study found that 30% of Olanzapine-treated schizophrenia patients gained 7% of their baseline body weight⁴. It has been observed that olanzapine has considerably higher effect on body weight as compared to all other antipsychotic medication except for clozapine⁵.

Our study showed that intervention group had a mean decrease of 2.62 kg with SD \pm 3.13 compared to control group with a mean decrease of 1.57 kg with SD \pm 2.83. These results are comparable with the findings of Jarskog LF et al¹⁰ in which results of experimental group and placebo were compared. Results from intervention group showed that patients on Metformin had less weight gain at 16 weeks follow up from baseline compared to weight gain in placebo group. Comparable results were also observed in alternative study conducted by Hoffmann VP et al¹³ in which the mean weight gain in patients with schizophrenia from baseline was 2.76 \pm 0.75 kg for Olanzapine only group compared to 0.65 \pm 0.63 kg for Olanzapine plus Metformin group. Our study results also show considerable similarity with the study of Baptista T et al¹⁴ in which the mean weight loss in the Metformin group was 2.8 + 3.2 compared to 1.4 + 2.6 kg in the Olanzapine only group.

One of the limitations in this study was that the duration of the study was short, and we did not follow up the changes of weight and body mass index after 12 weeks which makes it unclear whether the positive effects of metformin would be substantial over long periods.

Another limitation was small sample size which makes it difficult to generalize the results. One other limitation we had was that we did not assess the effects of diet and behavioral strategies as ideally these should be applied in combination with metformin to control the patients' body weight more effectively.

CONCLUSION

Mean increase in weight in patients who take Metformin along with Olanzapine is less than Olanzapine alone in the patients with schizophrenia.

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CONTRIBUTORS

MFK conceived the idea, wrote initial draft and executed the plan. SUH and KM helped refine the script, data collection and literature search. ZN supervised the project and provided guidance at all levels of the project.