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KEY WORDS:

A STUDY ON THE EFFECT OF METFORMIN COMBINED WITH INSULIN IN OVERWEIGHT PATIENTS WITH TYPE 1 DIABETES MELLITUS

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ABSTRACT

Many patients with type-1 diabetes (T1DM) have longstanding inadequate glycemic control, despite intensive insulin treatment. Metformin is an Oral Hypoglycaemic Agent that improves insulin action in Patients with type- 2 diabetes. In a randomized double blind cross over study , We investigated the effect of a 24 wk treatment with Metformin versus Placebo in overweight patients with T1DM and persistent Inadequate Glycemic control.

Methods: Double-blinded intervention with 850 mg thrice daily Metformin or Placebo daily in 108 overweight type 1 diabetic patients as adjunct to intensive insulin therapy. Primary endpoint was HbA1c, while secondary endpoints were profile of body weight, frequency of Hypoglycaemia, Blood pressure, Lipids, Total Insulin dosage and self-monitored Blood Glucose .

RESULTS: After 24 weeks, HbA1c was significantly lower after treatment with Metformin (7.6 ± 1.0%) compared with baseline(8.3± 1.2%, p <0.005) and Placebo (8.4±1.1% , p<0.005). Fasting blood glucose were significantly lower in Metformin group after 24 wks (8.4± 2.8 mmol/l) in comparison with baseline 12.3± 3.0 mmol/l; p<0.01) and Placebo after 24 weeks (12.6± 3.4 mmol/l; p<0.01). The Total Daily Insulin dose (IU) was significantly reduced in the Metformin group compared to placebo after 24 weeks (53.1 ±10units vs. 57.1± 14; p<0.05). A reduction in body weight was found using Metformin compared to Placebo (3.5 ± 1.2 vs. 0.9 ± 1.2, p<0.05). Lipids and Blood pressure did not differ significantly after intervention. Metformin, as adjunct to intensive Insulin therapy, was associated with a reduction in the total daily insulin dose and a significant weight loss in patients with type 1 diabetes mellitus.

CONCLUSION: Metformin can improve Glycemic control effectively, reduce Total Insulin dose and cause weight reduction in overweight people with type 1 diabetes mellitus.

ABBREVIATIONS: HbA1C glycosylated haemoglobin, BMI Body Mass Index, HDL High Density Lipoprotein, TGL Triglyceride, FBG Fasting Blood Glucose, SD Standard Deviation, ATP Adult Treatment Panel

INTRODUCTION

Observational studies (1,2) have shown that as the duration of diabetes increases, the prevalence of complications like retinopathy, neuropathy and nephropathy is highest in those with poor glycemic control and lowest in those with good control.

Metformin is a commonly used biguanide in the treatment of type 2 diabetes either as monotherapy or in combination with other oral hypoglycaemic agents or insulin. The drug has a glucose-lowering effect due to a reduced hepatic glucose production (inhibition of gluconeogenesis) and increased insulin-stimulated glucose uptake in skeletal muscle and Adipocytes .(3,4). Experience from studies with type 2 diabetic patients has shown that the use of Metformin compared to Treatment with Sulfonylurea or Insulin reduced the risk of macro-vascular diabetes-related complications . (5)

As the effect of Metformin on Glucose Metabolism is independent oF residual Beta cell activity (4), this drug has been considered a possibility for use in patients with type 1 diabetes. However, Addition of Metformin to Insulin therapy in Adults with type 1 Diabetes Mellitus has previously been assessed in a few trials. These studies suggested no significant reduction in HbA1c or body weight but demonstrated a reduction in daily Insulin dose of 7–25%.(6-10)

The aim of the present study was to investigate a possible beneficial effect of Metformin on Glycaemic control (Primary endpoint) as well as Insulin requirement, Body Weight in a group of type 1 Diabetic subjects with Poor Metabolic Control (secondary endpoints).

PATIENTS AND METHODS

This was a randomized, double blind, placebo controlled comparative cross over study evaluating the effect of metformin on blood glucose control in overweight patients with type 1 Diabetes Mellitus. The study was approved by local ethics committee.

Patients

All patients were c-peptide negative with serum c-peptide conc. <0.18 nmol/l at the time when blood glucose level was >5 mmol/l. All patients were diabetic for more than 1 year. All patients were overweight with a BMI> 25 kg/m2.

Study design

Study was done at Department of Medicine, Patna Medical College & Hospital, Patna during the period of October 2017 to September 2018 with a "screening visit" followed by a 4 wk "run-in" period, following which patient had a 24 wk treatment period. "Run in "period was for patient education, optimising insulin therapy and assessing patient ability to comply with study protocols. Then patient were prescribed either Metformin or Placebo for 24 wks along with Insulin after dividing them in two groups after randomising using a computer based sequence. The starting dose of metformin was 850mg/d and increased by 850mg per week to maximum 850 mg thrice daily. Thus from the third wk of study period , patients were receiving metformin 850mg or placebo thrice daily after meals. Patient continued to take usual Insulin brand and regimen throughout the period of the study. Phone contact was made weekly with all patients to facilitate insulin dose adjustment and to Enquire about the side effects. Patients were counselled to perform at least twice daily pre-Prandial domiciliary blood glucose measurement and to report the blood glucose level and Insulin doses in a diary. In the event of Hypoglycemia, Number of Episodes and level of Glucose were recorded.

Patients were reviewed every 4 weeks during the study and on each visit inquired about current Insulin Dose, any missed tablet and any side effects. On each visit, patients' height , weight and Blood pressure were recorded. After a minimum 8 hr overnight fasting, Blood samples were measured for Fasting Blood Glucose, HbA1C, Lipid profile, Liver and Renal Function Tests.

BIOCHEMICAL ANALYSIS

Blood samples for Plasma Glucose Value were collected into Sodium fluoride (2-3 gm/ml whole blood) and centrifuged to

separate the Plasma. Plasma Glucose was measured automatically using Hexokinase Method. Total cholesterol, HDL, TGL and HbA1C were measured.

STATISTICAL ANALYSIS

Primary endpoint was HbA1c, while secondary endpoints were Mean FBG, change in Insulin doses, number and severity of Hypoglycaemic Episodes, Effect on body weight, Blood pressure and lipid profile were measured. All the data were entered into a computer data base. Results were expressed as mean ± SD unless stated otherwise. Statistical analyses were performed on an intention to treat basis. P<0.05 was set to be statistically significant. Multiple group comparison was made by analysis of variance and two group comparison were performed with two tailored student paired t-test.

RESULTS

A total of 108 patients were eligible for the study after screening visit. After run in phase, 18 patients withdrew as a result of poor compliance. 90 patients completed the study. Baseline characteristics of 90 patients are shown in table 1.

72 patients were on Pre meal plus a Basal Bolus Insulin Regimen and 18 were on a Twice daily Insulin Injection Before meals {biphasic isophane human insulin(premix) 30% regular and 70% isophane insulin) (Mixtard 30, Novo Nordisk)}.

One or more features of Insulin Resistance or Metabolic Syndrome as per 2001 National Cholesterol Education Program (ATP)III.

METABOLIC CONTROL (HbA1C)

At the start of the study, Baseline HbA1C levels were comparable (8.3± 1.2% vs 8.7 ± 1.1%) in the Metformin and Placebo groups, But as the study progressed, HbA1C gradually decreased in the Metformin Group with no change in the Placebo group (7.6 ± 1.0 vs 8.4 ± 1.1%, p<0.005).

Table 1 . Clinical Characteristics Of Patients Studied.

PATIENT NUMBER	108
SEX MALE:FEMALE	8:7
AGE (YEARS)	38 ± 10
WEIGHT (KG)	90 ± 10
BMI	28.3 ±2.6
WAIST CIRCUMFERENCE	96 ±5
DURATION OF DIABETES (YRS)	19 ± 10
SERUM C- PEPTIDE (nmol/l)	0.09 ± 0.05
BASELINE HbA1C (%)	8.5 ± 1.2
PREMEAL BASAL INSULIN REGIMEN	72
TWICE DAILY INSULIN REGIMEN	18

FASTING BLOOD GLUCOSE

Baseline Fasting Blood Glucose Concentration were comparable (12.3 ± 3.0 mmol/l vs 12.5 ± 3.4 mmol/l) in the Metformin and Placebo Groups, But as the study progressed, Fasting Plasma Glucose Concentration gradually decreased on Metformin Treatment and Final Fasting Plasma Glucose following 24 wk Metformin Treatment was significantly lower compared with Placebo(8.4 ± 2.8 vs 12.6 ± 3.4 mmol/l , p<0.01).

INSULIN DOSAGES

At the start of the study, Total Daily Insulin Dosages levels were comparable (60 ± 14 U/d vs 60 ± 13 U/d) in the Metformin and Placebo groups, But at 24 weeks, A significant reduction in total daily Insulin dosages in the Metformin Group and Increase in the Total Insulin Dosage in the Placebo Group was seen (-5.9 ± 2.2 vs 2.9 ± 1.7, p< 0.004).

BODY WEIGHT

In the Metformin Group , A Mean Reduction in Body Weight of 3 ± 1 kg and a weight gain of 0.8 ± 1.1 kg in Placebo Group during the study period was seen. Corrected for baseline values, a significant difference in changes in Body Weight was found using Metformin compared to Placebo of -3.9 ± 1.5 kg., p<0.002)

INSULIN REGIMEN

There were no differences in HbA1C following Metformin or Placebo Treatment in Patients receiving either twice daily Insulin Regimen or with Basal Bolus Insulin Regimen. In both the groups , no significant difference were noted for the HbA1C levels (0.9 ± 0.1 vs 0.9± 0.5) or FPG levels (3.7 ± 0.1 vs 4.5± 0.4).

TABLE 2 : Baseline and final data following 24 weeks treatment with metformin or placebo in patients with type 1 Diabetes Mellitus

	METFORMIN		PLACEBO	
RESULTS	BASELINE	FINAL	BASELINE	FINAL
HbA1C (%)	8.3±1.2 %	7.6±1.0	8.7±1.1	8.4±1.1
FPG (mmol/l)	12.3±3.0	8.4±2.8	12.5±3.4	12.6±3.4
Insulin Dose (U/d)	60±14	53.1±10	60±13	57.1±14
Weight (kg)	87.6±2.7	84.6±3.2	92.0±2.1	92.9±2.6
Cholesterol (mmol/l)	4.92±0.18	4.83±0.17	5.19±0.13	5.22±0.14
TGL (mmol/l)	1.02±0.10	1.30±0.13	1.02±0.09	1.14±0.06
HDL (mmol/l)	1.58±0.06	1.55±0.06	1.57±0.08	1.62±0.12
LDL (mmol/l)	2.87±0.15	2.67±0.12	3.14±0.18	3.05±0.17

HYPOGLYCEMIA

Based on self-documented Hypoglycaemic Events in Patients diary, We found a significant increase in the frequency of Biochemical Hypoglycaemia in the Metformin Group compared to the Placebo Group (0.7 ± 0.9 vs. 0.3 ± 0.5 events/ patient/ week; P = 0.005). No severe events of Hypoglycaemia were reported.

LIPID PROFILE

The lipid profile did not differ significantly after the 24 wk study period or between the groups of Metformin or Placebo.

BLOOD PRESSURE

No significant difference in the blood pressure either systolic or diastolic after 24 wks of study was noted in the two groups.

ADVERSE EFFECTS OF THE DRUG THERAPY

Six patients complained of gastrointestinal side effects. 5 patients complained of nausea and vomiting in the metformin group while 1 from placebo group had those symptoms. No patients withdrew from the study in either groups due to the side effects and all completed the trial on Metformin 850 mg or Placebo One Tablet Thrice daily.

DISCUSSION

Metformin therapy is not conventionally used in the treatment of type 1 diabetes, and the use of Metformin along with intensive Insulin therapy has been studied less frequently in type 1 Diabetes Mellitus than in type 2 Diabetes Mellitus. This double-blinded, placebo-controlled study of overweight Adult subjects with poorly controlled Type 1 Diabetes demonstrated a Beneficial Effect on body weight and Total Daily Insulin dose by using Metformin as adjunct to Intensive Insulin Therapy. Previously, Two Placebo-Controlled Paediatric studies of poorly controlled type 1 diabetic patients found a significant improvement in HbA1c in the Metformin Group achieved at lower daily Insulin Dosages [11,12]. According to most previous reports, no significant improvement in HbA1c after optimised glycaemic regulation and addition of Metformin neither after 12 nor 24 weeks have been found, But our study showed that HbA1C gradually decreased in the Metformin Group with no change in the placebo group (7.8 ± 1.1 vs 8.6 ± 1.2%, p<0.005) after 24 weeks of the trial. A recently published study similar to our study by Khan et al. found a significant reduction in HbA1c from 8.5 to 7.8 (baseline versus 6 months) (P < 0.005), a significantly lower fasting Blood Glucose level (12.4 vs. 8.3 mmol/l), and a significantly lower total daily Insulin dose using Metformin (60 ± 14 vs. 50 ±13 units) (P < 0.05) compared to placebo following 16 weeks of treatment [13].

The insulin-sparing effect of Metformin in Adults has been described in a few trials and in general a reduction in total daily Insulin requirement of about 16% was seen [6,7,8,9,15–16].

Previous data support a beneficial effect of adding Metformin to Intensive Insulin therapy in subjects with type 1 Diabetes requiring high dosages of Insulin as reviewed in 1997 by Daniels and Hagmeyer [14]. Our data also demonstrated a significant reduction in the total daily Insulin dosage of nearly 10% in the group receiving Metformin as adjunct to Insulin therapy compared to Placebo which is consistent with the previous reports [7,9,13-15]. The Insulin-sparing effect in our study could be related to an improvement in Insulin sensitivity, as some of the subjects attending were overweight and required large amount of insulin.

Our data showed that the incidence of Hypoglycaemia, in patients receiving Metformin, was increased. This effect was most explicit in the first 2 months of the study and might be explained by the more frequent adjustment of Insulin dose according to a predefined algorithm and hence an increase in Insulin administration. Further, a reduced Gluconeogenesis in the Metformin Group could potentially reduce the counter regulatory response to Hypoglycaemia.

Our results demonstrated a significant difference in body weight of nearly 4 kg using Metformin compared to placebo after 24 weeks. The large dose of Metformin (850mg thrice daily), the remarkable reduction of 10% in the total daily Insulin dose as well as the suppressed appetite (frequently reported by the patients) might explain the significant weight loss in our study. Previous reports used 500 mg or 850 mg Metformin twice daily, but on the relatively high dose of metformin in our study, we did not register more adverse events than in other studies with lower doses.

Lipid profiles did not differ significantly between the Metformin and Placebo groups in our study which is consistent with most previous reports [8,11,15]. A placebo-controlled study from 2001 (Lacigova et al.) although found a reduction in free fatty acids during clamp as well as improved glycaemic control. We found a reduction in body weight and daily insulin requirements by adding metformin to intensive insulin therapy.

Clinical Risk factors like Hypertension, Abdominal Obesity, High Triglycerides, low High-Density lipoprotein levels and increased Blood Pressure could be used to identify subjects with type 1 Diabetes Mellitus who were Insulin Resistant.The symptoms were united in Insulin Resistance Syndrome and the factors alone or in combination can increase the risk of coronary heart disease [17]. Hypertension is a well known risk factor in type 1 Diabetes and for Heart Disease., often related to underlying Nephropathy. We examined for any possible Blood Pressure lowering Effect of Metformin during a 24-hr Blood Pressure monitoring but found no significant difference, day or night, between the Metformin and the Placebo Groups consistent with a previous report [9]. It needs to be mentioned though that most of the out-clinic patients prior to inclusion were Normotensive in our study and had been treated with ACE-inhibitors for some time earlier.

CONCLUSION

In overweight and poorly controlled type 1 Diabetes Mellitus, Metformin as an adjunct to Insulin Therapy reduces the total Insulin requirement, provides a significant improvement in HbA1C and reduction in weight . There is a small risk of Hypoglycaemic Events in patients with poorly controlled Diabetes Mellitus. Based on this and other studies, Metformin may be beneficial specifically in overweight Insulin Resistant type 1 Diabetic subjects with a need for large daily Insulin requirements. Further studies are needed to address if Metformin treatment reduces the risk of other Microvascular and Macrovascular complications in patients with type 1 Diabetes Mellitus.

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