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EFFECT OF METFORMIN AS AN ADD ON THERAPY TO TYPE 1 DIABETES MELLITUS

Medicine

KEYWORDS:

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ABSTRACT

AIM OF THE STUDY To evaluate whether the addition of metformin to insulin and standard diabetic management in uncontrolled type 1 diabetic patients will results in lower insulin dosage, lower glycosylated haemoglobin, and fasting glucose. **METHODOLOGY** In a prospective randomized conrol study 52 patients with uncontrolled type 1 diabetes with no contraindication for metformin therapy who attended diabetic clinic and medicine OP of Medical College, Trivandrum, were divided into 2 groups. One group received the usual insulin regime for the control of DM and the other group received metformin in addition to the insulin treatment. The primary outcome was effective control of fasting and post prandial blood sugar. **RESULTS** Analysis of all the subjects completing the trial demonsrated significant (P<0.05) improvement in HbA1c of 0.5% in the metformin group. Compared to insulin only group. There was decrease in glycosylated haemoglobin of 1.8 +o 0.68 units in the metformin group. Compared to the insulin in only group and a decrease 1.382 + 0.741 in the insulin only group. **CONCLUSION** Thus the present study indicate that metformin when added to insulin in uncontrolled type 1 diabetes mellitus improves insulin sensitivity.

INTRODUCTION

Diabetes mellitus is one of the oldest diseases affecting man. Ever since its description this disease and the widening spectrum of its complications have been the field of intense interest and study. In dealing with chronic disease like diabetes, management strategies should ideally aim at preventing the long term complications or atleast. Intervening early to prevent their progression. Several trials have shown that a strict glycemic control reduced clinically important progression of complications. Thus the relationship between good glycemic control and the prevention of diabetic complications in patients with type 1 diabetes mellitus. Is well established in the light of the above study the field of interest has been diverted to methods of attaining strict glycemic control in tpe 1 diabetes mellitus. It is in this contest that the effect of metformin as an adjunct therapy in uncontrolled type 1 diabetes mellitus gains importance. There have been some studies in the west on the effect of metformin in uncontrolled type 1 diabetes mellitus. The present study is an effort to evaluate the effect of metformin in type 1 diabetes mellitus in the Indian setup.

MATERIALS AND METHODS

Selection of patients :

The present study included 52 patients chosen from inpatient and out patient department from Medical College, Trivandrum in the year 2001 November to 2003 November. Those paitents who were detected to have diabetes mellitus before 15 years of age and those with c peptide level <0.17 picomol/l were chosen for the study. All the patient had a suboptimal metabolic control as evidenced by glycosylated haemoglobin >8% and insulin dosage > IU/kg/day for prior 1 month. The exclusion crieraia for the study included serum creatinine >2mg%, proliferative retinopathy, hepatic dysfunction, > 3 episodes of diabetic ketoacidosis / year, cardiac dysfunction or another serious coexisting medical illness.

Protocol

The protocol was approved by research ethical committee of Medical College Hospital, Trivandrum. Written informed consent was obtained from all participants or from the parents in case the patients were minor.

Subjects underwent a 1 month run in period to screen for complications, to update patient education, optimize insulin therapy (all patients were started on human insulin), and to assess the subjects ability to comply with the protocol. At the end of the run in period subjects were randomized either to the metformin + insulin group or to insulin only group. The subjects were assessed every 2 weeks during the 3 months active phase. Medication ie metformin was given with meals to minimize gastro intestinal tract side effects. Starting dose was 500mg/day (at breakfast) and was increased by 500 mg/day every 2 weeks to a maximum of 1000mg/day for those weighing <50kg and 1500 mg/day for those weighing 50 to 75mg, during the 2 weekly visits fasting and post prandial blood sugars (after insulin and food) were measured and insulin dosage was adjusted in the insulin group (10% increments or decrements to keep blood sugar in the target range. In the insulin + metformin group the metformin dosage was increased and insulin dosage was reduced to keep blood sugar in the target range (4-8mmol/l). Phone contact was made weekly with the study subjects for review of side effects and to facilitate insulin dose adjustment. At each visit every 2 weeks height, weight, body mass index, blood pressure, were performed to monitor side effects. Estimation of creatinine and liver enzymes were made monthly.

Estimation

Glycosylated haemoglobin was done at the start of intervention and at the end of the study.

Statistical Analysis

A total of 52 patients were selected for the present study. Comparisons between the insulin only group and insulin + metformin group for the variables like age group, duration of diabetes, body mass index, glycosylated haemoglobin, insulin dosage, fasting plasma glucose using Student's t test. Associations between the variables were found out by employing Chi square statistics. Statistical analysis performed using SPSS 10 software for windows.

RESULTS

Table - 1

Baseline demographic an clinical characteristics of the study group

	Insulin only	**Insulin + Metformin**
Number of patients	28	24
Age (mean in yrs)	20.3 ± 1.4	19.4 ± 1.8
Sex Male Female	16 12	9 15
Duration of diabetics	11.9 ± 2.2	10.9 ± 3.2
Weight (kg)	44	42.5
BMI (kg/m^2)	22 ± 1.2	19 ± 1.8
HbA 1c (%)	9.41 ± 1.52	10.64 ± 1.70
Insulin dosage (units /kg/day)	1.6 ± 0.8	1.2 ± 0.28
Initial FPG (mg/%)	220 ± 2	240 ± 2.5

Age distribution of the patients in the two study groups

Age groups of patients	Insulin only	Insulin + Metformin
< 20 yr	15 (28.8%)	12 (23.01%)
20 – 29 yr	7 (13.46%)	9 (17.3)
30.34 yr	5 (9.6%)	3 (5.7%)
40-49	1 (1.9%)	0

Change from baseline after months of treatment

	Insulin only	Insulin + Metformin
Number	28	24
Age	20.3 ± 1.4	19.4 ± 1.8
Sex Male Female	16 12	9 15
BMI	22 ± 1.4	19 ±1.8
HbA1c	8.028 ± 2.28	9.25 ± 1.93
Insulin dosage (units /kg/day)	1.21	0.62

Change from baseline after 3months

Characteristics	Insulin only	Insulin + Metformin	Significance
Hb A1c (%)	1.38s1 ± 0.07	1.8 ± 0.68	P<0.05
Insulin dose (U/kg/day)	0.82 ± 0.2	- 0.6 ± 1	P <0.001

Group statistics

	Groups	No. of patients	Mean	SD
HbA1c	Insulin only	28	9.41	1.52
	Insulin + Metformin	24	10.64	1.70
HbA1c (after 3 months)	Insulin only	28	8.028	2.28
	Insulin + Metformin	24	9.25	1.93
Initial insulin	Insulin only	28	43.39	10.87
	Insulin + Metformin	24	48	9.8
Final insulin	Insulin only	28	46.39	10.95
	Insulin + Metformin	24	24.87	6.64
Hb A1c (%)	Insulin only	28	1.38	0.74
	Insulin + Metformin	24	1.80	0.68
Insulin	Insulin only	28	19.55	12.9
	Insulin + Metformin	24	111.92	44.09
Body weight	Insulin only	28	37.7	10.20
	Insulin + Metformin	24	14.8	6.97

The study group included 52 patients. The inclusion criteria was setout to minimize the likelihood of recruiting subjects with type 2 diabetes mellitus and also those patients who are contraindicated for metformin therapy like renal failure and hepatic dysfunction. Insulin sensitivity was not done in the present study due to technical reasons. But an indirect evidence of insulin resistance was obtained through the measurement of glycosylated haemoglobin, insulin dosage and fasting glucose. Compared to insulin only group, age body mass index and HbA1c were comparable between the 2 groups. T table 1 shows the baseline demographic data of all subjects. There was a decrease in glycosylaed haemoglobin of 1.8 +0068% in the metformin group. In the insulin only group a decrease of 1.382 + 0.741% was seen. Thus the trial demonstrated significant ($p<0.05$) improvement in HbA1c of 0.5% in the metformin group when compared to the insulin only group. Table 2 shows the change from baseline after 3 months trial.

Metformin treated subjects required significantly lower insulin dosage on a unit/ kg basis compared to the other group. There was 48.18% (43 units to 24 units) decrease in insulin dosage in the metformin group and 6.18% increase in insulin dosage in the insulin only group. The initial fasting blood sugar in the insulin only group was 220 + 2mg% and in the metformin group was 240 + 3mg% final fasting blood sugar in the insulin only group was 154 + 2.8mg% and that in the insulin + metformin group was 160 + 2.5mg%. The decrease in fasting blood sugar in both groups were significant there was significant reduction of 48.18% insulin dosage in the metformin group.

DISCUSSION

In the diabetic control and complications trial clearly demonstrated that intensive insulin therapy to achieve heal normal glycemia reduces the risk of development and progression of long term complication of type 1 diabetes mellitus but lead to an increase in hypoglycaemic episodes. Metformin is a biguanide that has been used in the management type 2 diabetes for > 40 years. It improves glycemic control by enhancing insulin sensitivity. In type 1 diabetes mellitus patients the addition of metformin to insulin therapy has been assessed in a few trials involving few paients with uncontrolled type 1 diates mellitus. These studies suggested a mean reduction in insulin resistance. The present study was an attempt to evaluate the effect of metformin on blood glucose control and insulin dosage in uncontrolled type 1 diabetes. The study indicates that addition of metformin to insulin in uncontrolled type 1 diabetes mellitus in improves insulin sensitivity. The change in glycosylated haemoglobin and insulin dosage produced by metformin could be partly due to change in growth hormone secretion. But this can only explain the effect of metformin in adolescents with type 1 diabetes mellitus. The effect of metformin even in elder type 1 diabetics could be due to other effects of metformin like decreased hepatic glucose output and increase in insulin binding to receptors.

CONCLUSION

Majority of patients of type 1 diabetes are of poor socioeconomic status. Most of them cannot afford lifelong insulin treatment. Many of them stop insulin therapy due to the cost of treatment. The present study demonstrated that targeting insulin resistance with metformin, traditionally used to treat type 2 diabetic patients. Significantly improves metabolic control in uncontrolled type 1 diabetic patients and represents a novel adjunctive therapy in uncontrolled type 1 diabetic patients worthy of further investigation. This fact is very interesting and helpful in the setting of poor socio economic status of the Indian patients.

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