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COMPARATIVE STUDY OF EFFECT OF ALPHA GLUCOSIDASE INHIBITORS – MIGLITOL, ACARBOSE AND VOGLIBOSE ON POSTPRANDIAL HYPERGLYCEMIA AND GLYCOSYLATED HEMOGLOBIN IN TYPE-2 DIABETES MELLITUS

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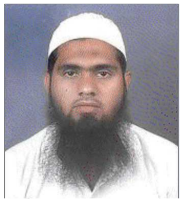
ABSTRACT

Diabetes mellitus has emerged as a major healthcare problem in India. Management of postprandial plasma glucose (PPG) level is important to prevent the complications associated with type-2 diabetes. Considering paucity of studies motivated us to compare the effect of Acarbose, Miglitol and Voglibose on postprandial hyperglycemia and HbA_{1C} . It was single blind, randomized, parallel group, comparative, prospective clinical trial on 90 diabetes type 2 patients defined as post prandial plasma glucose (PPG) levels more than 200 mg % and glycosylated haemoglobin more than 7 % at visit 1. Glycosylated hemoglobin (p=0.78) and post prandial blood glucose (p=0.61) was reduced more by Voglibose than Miglitol and Acarbose. Though this finding is not statistically significant, adverse effect profile was better with Voglibose (6.66%) than Miglitol (16.66%) and Acarbose(33.33%). Present study recommends use of Voglibose looking at its efficacy and safety profile as preferential choice in the management of postprandial hyperglycaemia in treatment of type-2 diabetes mellitus.

KEYWORDS: ***Postprandial hyperglycemia, Miglitol, Acarbose, Voglibose, Glycosylated haemoglobin***



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INTRODUCTION

Diabetes mellitus has emerged as a major healthcare problem in India. According to Diabetes Atlas published by the International Diabetes Federation (IDF), there were an estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people by 2025. WHO estimates that diabetes, heart disease and stroke together will cost about $ 333.6 billion over the next 10 years in India alone. The real burden of the disease is however due to its associated complications which lead to increased morbidity and mortality[1].

Poor control of hyperglycemia appears to play a significant role in the development of cardiovascular disease and related complications in diabetes.[2] Recently, there has been an increasing evidence that the postprandial state is an important contributing factor in the development of atherosclerosis.[3]

Evidence that tight glycemic control helps to prevent complications in type-2 diabetes is also accumulating.[4,5] Postprandial hyperglycemia is also one of the earliest abnormalities of glucose homeostasis associated with type 2 diabetes and is markedly exaggerated in diabetic patients with fasting hyperglycemia.[6] Moreover, it appears that management of postprandial plasma glucose (PPG) levels, rather than fasting plasma glucose (FPG) levels, is important to prevent the complications associated with type-2 diabetes.[7,8]

Alpha glucosidase enzyme plays an important role in digestion of complex carbohydrates by cleaving oligosaccharides into monosaccharides. AGIs compete with the oligosaccharides for the binding site. They are classic competitive inhibitors. The mechanisms of action of the different AGIs are similar though not identical. Acarbose is also an inhibitor of intestinal sucrase and pancreatic amylase. Voglibose inhibits most alpha glucosidase enzyme but is weaker than Acarbose at inhibiting sucrase and has little effect on pancreatic amylase. Neither Acarbose nor Voglibose interferes with glucose absorption through the intestinal sodium dependent glucose transporters. Miglitol is effective AGIs and has greater activity than Acarbose on isomaltase. It has no effect on pancreatic amylase but does mildly interfere with glucose absorption by interacting with the intestinal sodium dependent glucose transporters.[9]

Considering the availability and effectiveness of all these agents the present study was thus aimed primarily to compare the effect of Acarbose, Miglitol and Voglibose on postprandial hyperglycemia and HbA_{1C} and then to suggest which alpha glucosidase inhibitor will be an ideal agent to be preferred in the management of postprandial hyperglycemia in type-2 diabetes mellitus.

MATERIAL & METHODS

The study was single blind, randomized, parallel group, comparative, prospective clinical trial in patients of type II diabetes mellitus carried out by the Department of Pharmacology, Government Medical College, Aurangabad in collaboration with Department of Medicine.

Ninety patients (n = 90) of type II diabetes defined as post prandial plasma glucose (PPG) levels more than 200 mg % and glycosylated haemoglobin more than 7 % at visit 1, were enrolled in study provided they were ready to give written informed consent and had a history of type 2 diabetes mellitus for 6 months or more not controlled by dietary measures and exercise.

The exclusion criteria for patients were presence of type-1 diabetes mellitus, requirement of insulin for diabetic control, allergy to study drugs, deranged liver or kidney function tests, diabetic complications, unwillingness to give informed consent, pregnant and lactating females, history of anti-diabetic medication other than study drugs

during past 3 months, presence of gastrointestinal disease like inflammatory bowel disease, large hernias, intestinal obstruction, active ulcers or chronic pancreatitis. Concomitant medication effecting glucose homeostasis like glucocorticoids within past 8 weeks, uncontrolled thyroid function, any other investigational drug or participating in clinical study within 8 weeks before screening.

Approval of the institutional ethics committee was taken prior to the start of study. 300 patients of type 2 diabetes were screened out of which 90 were enrolled in the study after satisfying the inclusion and exclusion criteria. Included patients were explained in detail about the study pattern and related hazards. Those included under went all baseline investigations like complete blood count, liver function tests, kidney function tests, blood sugar level, and Glycosylated Hb, at the start of the study and at the end of the study. Enrolled patients were divided into three groups of thirty each by computer generated randomization chart (calculated from True Epistat, Standard version 1999). Group-1 patients received Tab. Miglitol 25 mg T.D.S with first bite of major meals for duration of one month and 50 mg T.D.S with first bite of major meals for another three months.Group 2 patients received tablet Acarbose 25 mg T.D.S with first bite of major meals for duration of one month and 50 mg T.D.S with first bite of major meals for another three months. Group 3 patients received Tab. Voglibose 0.2 mg T.D.S with first bite of major meals for a period of one month and then 0.3 mg T.D.S with first bite of major meals for a period of 3 Months. To assess the compliance patients were asked to visit the diabetic clinic for follow up and collection of drugs every fifteen days with remaining tablet strips. At each follow up visit, patients were assessed for glycemic control (blood sugar level); history pertaining to adverse drug effect was also asked and all patients were given advice about diet and exercise.

The Primary efficacy measures for the study were change in post prandial blood glucose level from baseline to end of study (16 weeks) and change in Glycosylated haemoglobin (HbA1C) from baseline to end of study. The secondary efficacy measure was Change in fasting blood glucose from baseline to end of study. For comparing the effect of Miglitol, Acarbose and Voglibose on blood sugar level and HbA_{1c} before and after therapy, Paired "t" – test was carried out. For intergroup comparison, unpaired "t"– test was carried out. Data was analysed using SPSS software

RESULTS AND OBSERVATIONS

In present study, ninety patients (n=90) of type – 2 diabetes mellitus completed the study. A comparative evaluation of Miglitol, Acarbose and Voglibose on postprandial hyperglycemia and glycosylated hemoglobin was done. All the groups were matched in baseline characteristics i.e. age, sex and weight.

The mean glycosylated hemoglobin *(Table 1)*, post prandial blood glucose *(Table 2)* and fasting blood glucose levels *(Table 3)* decreased significantly when compared to baseline value in all three groups .

Table 1
Comparative effect of Miglitol, Acarbose and Voglibose on glycosylated Haemoglobin (HbA_{1c}) (before and after therapy)

Group	HbA_{1C} (%) (Mean value ± SD)		P value
	Before therapy	After therapy	
I	8.92 ± 1.65	7.20 ± 0.92**	P < 0.001
II	9.79 ± 1.68	8.65 ± 1.49**	P < 0.001
III	9.25 ± 1.24	7.68 ± 0.80**	P < 0.001

Note: P < 0.001: Statistically highly significant**
Group I : Miglitol Group II : Acarbose Group III : Voglibose

Table 2
Comparative effect of Miglitol, Acarbose and Voglibose On postprandial blood glucose levels (Before and after therapy)

Group	Postprandial blood sugar levels [mg%] Mean value ± SD		P value
	Before therapy	After therapy	
I	245.16± 78.95	158.53± 18.07**	P < 0.001
II	242.76± 48.71	184.30± 44.46**	P < 0.001
III	253.03± 59.30	159.30 ± 29.20**	P < 0.001

Note: P<0.001** : Statistically highly significant
Group I : Miglitol Group II : Acarbose Group III : Voglibose

Table 3
Comparative effect of Miglitol, Acarbose and Voglibose On fasting blood glucose levels
(Before and after therapy)

Group	Fasting blood glucose levels [mg%] Mean value ± SD		P value
	Before therapy	After therapy	
I	130.86 ± 58.30	102.83 ± 21.14**	P < 0.001
II	126.86 ± 24.65	105.10 ± 13.45**	P < 0.001
III	130.56 ± 26.03	109.13± 12.24*	P < 0.05

Note: P< 0.001: Statistically highly significant; P<0.05* : Statistically significant**
Group I: Miglitol Group II: Acarbose Group III: Voglibose

INTERGROUP COMPARISON

A. Miglitol and Acarbose:

Inter group comparison between Miglitol and Acarbose showed that mean reduction in glycosylated hemoglobin was more in Miglitol group (1.71 ± 0.05) as compared to Acarbose (1.14 ± 1.07) using unpaired t – test and was found to be statistically significant with a p value < 0.05. Inter group comparison between Miglitol and Acarbose showed that mean reduction in postprandial blood glucose was more in Miglitol group (86.63 ± 67.03) as compared to Acarbose (58.46 ± 21.41) using unpaired t–test and was found to be statistically significant with p value < 0.05. Inter group comparison between Miglitol and Acarbose showed that mean reduction in fasting blood glucose was more in Miglitol group (28.03 ± 37.15) as compared to Acarbose (21.76 ± 11.20) using unpaired t–test and was not statistically significant with p value = 0.55.

B. Acarbose and Voglibose

Inter group comparison between Acarbose and Voglibose showed that mean reduction in glycosylated hemoglobin was more in Voglibose group (1.79 ± 1.06) as compared to Acarbose (1.14 ± 1.07) using unpaired t–test and was found to be statistically significant with p value < 0.05. Inter group comparison between Voglibose and Acarbose showed that mean reduction in postprandial blood glucose was more in Voglibose group (93.73 ± 39.37) as compared to Acarbose (58.46 ± 21.41) using unpaired t–test and was found to be statistically significant with p value < 0.05. Inter group comparison between Voglibose and Acarbose showed that mean reduction in fasting blood glucose was almost equal in both Voglibose group (21.43 ± 13.78) and Acarbose (21.76 ± 11.20) using unpaired t–test and p value calculated was equal to 0.55.

C.Miglitol and Voglibose

Inter group comparison between Miglitol and Voglibose showed that mean reduction in glycosylated hemoglobin was more in Voglibose group (1.79 ± 1.06) as compared to Miglitol group (1.71 ± 0.05) using unpaired t–test and was not statistically significant with p value =0.78. Inter group comparison between Miglitol and Voglibose showed that mean reduction in postprandial blood glucose was more in Voglibose group (93.73 ± 39.37) as compared to Miglitol group (86.63 ± 67.03)using unpaired t–test and was not statistically significant with p value = 0.61. Inter group comparison between Miglitol and Voglibose showed that mean reduction in fasting blood glucose was more in Miglitol group (28.03 ± 37.1) as compared to Voglibose group (21.43 ± 13.78) using unpaired t–test and was not statistically significant with p value = 0.65.

ADVERSE EFFECTS

Most common adverse drug reaction reported in all the three groups were related to gastrointestinal disturbances.

In the Miglitol group 5patients (16.66%), Acarbose 10 patients (33.33%) and 2 patients (6.66%) in Voglibose group had shown adverse drug reactions. In Miglitol group, gastrointestinal adverse drug reaction seen were, nausea in 1 patient (3.33%), flatulence in 2 patients (6.66%), diarrhoea in 1 patient (3.33%) and abdominal pain in 1 patient (3.33%). In Acarbose group, adverse drug reaction seen were, nausea in one patient (3.33%), flatulence in 6 patients (20%), diarrhoea in 2 patients (6.66%) and abdominal pain in 1 patient (3.33%). In Voglibose group, adverse drug reaction seen was flatulence in 2 patients (6.66%)

DISCUSSION

Nowadays patients of diabetes mellitus have been flourishing because of too many factors

like sedentary lifestyle and genetics etc. Post prandial hyperglycemia is considered to be major contributory factor for macro and micro vascular complications. So there is need of effective drugs which can control this culprit parameter.

The objective of the present study therefore was to compare the effect of Miglitol, Acarbose and Voglibose on postprandial hyperglycemia and glycosylated haemoglobin in type-2 diabetes patients.

The present study showed that Miglitol in the dose of 25 mg three times a day (TID) with first bite of meal for 4 weeks followed by 50 mg TID for another 12 weeks leads to statistically significant reduction in postprandial plasma glucose (PPG) level and fasting plasma glucose (FPG) level as well as glycosylated hemoglobin levels (HbA_{1c}). These results of Miglitol are in accordance with the study carried out by Fehman H.C. et al from October 1999 to August 2000.[10]

The results with Acarbose 25 mg TID for 4 weeks followed by 50 mg TID for another 12 weeks showed that there was significant reduction in glycosylated Hb as well as postprandial blood glucose level and fasting glucose level. These studies of Acarbose are consistent with study conducted by Department of Clinical Pharmacology, Chinese University Hong Kong, Prince of Wales hospital Shatin China.[11]

The results with Voglibose 0.2 mg TID for 4 weeks followed by 0.3 mg TID for 12 weeks also showed the significant reduction in HbA_{1c}, PPG and fasting blood glucose. Similar results were noted in the study conducted by Makumoto et al 1998 and Saino etal 1998.[12,13]

When Miglitol group was compared with Acarbose group, it was found that Miglitol has greater mean reduction in PPG level and glycosylated Hb and difference was statistically significant ($p<0.05$). Miglitol also has greater mean reduction of fasting blood glucose level as compared to Acarbose but difference was not statistically significant ($p=0.55$).

When Acarbose group was compared with Voglibose group, it was found that Voglibose has greater reduction in PPG level and glycosylated hemoglobin and difference is statistically significant ($p<0.05$). Effect on FPG level is almost similar ($p=0.96$). The results of the presence study does not substantiate with the claim of the study conducted by Vicharant et al who found that Voglibose (0.2mg) and Acarbose (100mg) were equally efficacious but Voglibose is associated with less adverse drug reaction (ADR) [14]

When Miglitol group was compared with Voglibose group, it was found that Voglibose has greater mean reduction in PPG levels and glycosylated haemoglobin but difference was not significant ($p>0.05$). These results are accordance with study conducted by Van de Laar F.A. et al [15].

As expected most common adverse effect in all three groups was gastrointestinal side effects like diarrhoea, flatulence, nausea and abdominal pain. But there were very less ADR in Voglibose group (6.66%) as compared to Miglitol (16.66%) and Acarbose group (33.33%). These results are accordance with Cochrane review of alpha-glucosidase inhibitors 2007.[16]

CONCLUSION

In the present study, all three alpha glucosidase inhibitors Miglitol, Acarbose and Voglibose have proven efficacy in reducing fasting as well as postprandial blood glucose level and HbA_{1c} level. Miglitol and Voglibose have equal efficacy in reducing postprandial blood glucose level and HbA_{1c} level but significantly better than Acarbose. The clinical benefit of Voglibose was its better safety profile as compared to Miglitol and Acarbose.

Thus, to conclude, the present study recommends use of Voglibose looking at its efficacy and safety profile amongst the available Alpha glucosidase inhibitors as preferential choice in the management of postprandial hyperglycaemia in treatment of type-2 diabetes mellitus

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