



# A COMPARATIVE STUDY OF MIGLITOL AND ACARBOSE ADD ON THERAPY INTENDED FOR BETTER GLYCAEMIC CONTROL IN TYPE 2 DIABETES MELLITUS

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## ABSTRACT

**Objectives:** This study was done to find out the comparative efficacy of Miglitol and Acarbose as add on therapy in patients of type 2 Diabetes Mellitus.

**Methods:** This is a prospective, randomized, patient controlled, open label comparative study involving Type 2 diabetes patients, aged between 35-70 years of either sex of hyperglycaemic with PPBS >180mg%, FBS <200mg% even after treatment with glimeperide 4mg and Metformin 2g for at least 3 months.

**Results:** Miglitol produced a mean reduction of PPBS of  $34.12 \pm 4.89\%$  and Acarbose produced a mean reduction of PPBS of  $30.61 \pm 5.86\%$  whereas reduction in HbA1C with Miglitol was  $0.58 \pm 0.05\%$  and that of Acarbose was  $0.47 \pm 0.09\%$ . The P value in both the cases were  $> 0.05$  signifying Miglitol to be better than Acarbose in terms of glycaemic control in type 2 D.M.

**Conclusions:** Type 2 Diabetes forms a significant share of the Diabetic load in India where cereals in the form of carbohydrates form the staple diet of most Indians. Thus  $\alpha$  glucosidase inhibitors like Miglitol and acarbose are sure to play an important role as an add on therapy when first line drugs like sulphonylurea and biguanides fail to control the hyperglycaemia and they have minimum adverse effects, with more or less similar efficacy with Miglitol being better than Acarbose.

**Key Words:** Type 2 Diabetes Mellitus, Hyperglycaemia, PPBS, HbA1c, Miglitol, Acarbose

## INTRODUCTION

Type 2 diabetes mellitus is a large and growing health problem and appears to be associated with urbanization, sedentary lifestyle and dietary habit. The World Health Organization (WHO) has estimated that the global prevalence of type 2 diabetes is increasing rapidly and India bears a sizeable burden of this epidemic.

The term diabetes mellitus describes a metabolic disorder of multiple etiology, characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both<sup>1</sup>. Type 2 diabetes mellitus is a progressive disease

and once diagnosed, the treatment pathway involves an increasingly complex combination of treatments as the disease worsens<sup>2</sup>. Therapy however should be individualized according to the degree of hyperglycaemia<sup>3</sup>.

There are three modalities to Diabetes care. First is aimed at lifestyle modification including physical activity and dietary restrictions. Second involves use of drugs which increase insulin availability like sulphonylurea or insulin secretagogue Repaglinide. Third modality is use of agents that increase insulin sensitivity like Biguanides and Thiazolidinedione or drugs which reduce insulin requirement like  $\alpha$  glucosidase inhibitors<sup>3</sup>. Compared with sulphonylurea, AGIs seem to be inferior with respect to glycemic control, but they reduce

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fasting and postprandial blood glucose as well as insulin levels<sup>4</sup>.

The primary objective in the management of type 2 diabetes is glycaemic control along with management or prevention of micro and macro vascular complications. Epidemiological evidence strongly implicates postprandial hyperglycaemia, but not fasting hyperglycaemia, as an important contributor associated with the development of macrovascular complication in type 2 DM<sup>5</sup>. Techniques that can improve postprandial control include lowering the carbohydrate, encouraging physical activity after meals, adding  $\alpha$  glucosidase inhibitors with meals and using rapidly acting insulin analogues<sup>5,6</sup>. Alpha glucosidase inhibitors (acarbose, miglitol and voglibose) are agents which specifically target post prandial blood sugar level<sup>7</sup>. When administered along with the first bite of a carbohydrate rich diet, carbohydrate absorption is shifted more distally in the intestine, allowing the sluggish insulin secretory dynamics of Type 2 diabetics to catch up with the carbohydrate absorption, thereby counteracting the post absorptive glucose rise<sup>8</sup>. These oral antidiabetic agents also have action on the fasting blood glucose level, gastrointestinal hormones and body weight. Thus their efficacy and safety needs to be compared for their therapeutic applications.

## MATERIALS AND METHODS

A prospective, randomized, patient controlled, open label comparative study was done on 50 Type 2 diabetes mellitus patients attending the Diabetic OPD at R.G.KAR Medical College and Hospital starting from July, 2004 and completed with 18 months' follow for each patient, up till May, 2006. Type 2 diabetes patients, aged between 35-70 years, of either sex, hyperglycaemic with PPBS >180mg%, FBS <200mg% even after treatment with glimeperide 4mg and Metformin 2g for at least 3 months, were taken into study after proper consent and ethical clearance from the local Ethical Committee.

Patients with abnormal LFT, blood urea or creatinine levels, with h/o inflammatory bowel disease, peptic ulcer, carcinoma, irritable bowel syndrome, any other concurrent drug therapy or life threatening complications, pregnant or lactating were excluded from the study. Type-1 Diabetes patients and Type-2 Diabetes patients on monotherapy or multi-drug therapy with other drug combinations/insulin therapy were also excluded from the study. Sample size was estimated to be 50 with 25 patients in each arm.

At the first visit, patients' history, general clinical examination, fasting and post-prandial blood sugar levels (assessed by standard glucose oxidase method] and HbA1C levels were noted.

Selected patients were randomly assigned in 1:1 ratio to ei-

ther of two groups, (25 each). 25 such patients [group A] were advised to take 25mg Miglitol twice daily along with first bite of food at lunch and dinner while 25 patients (group B) were advised to take 25mg acarbose twice daily along with first bite of food at lunch and dinner, as add on therapy.

Patients of each group were advised to attend OPD regularly at 8-12 weekly intervals, with FBS and PPBS reports for dose titration of the test drugs as required. The other parameters like HbA1c, urea and creatinine, blood aspartate transaminase and blood alanine transaminase levels were assessed at 3-6 monthly interval at their follow up visits. Patients with any abnormality regarding blood urea / creatinine, AST or ALT levels were excluded from the study.

According to PPBS levels, in follow up visits, the frequency of the  $\alpha$  glucosidase inhibitor was increased to thrice daily or dose titrated upto 50mg. History of any flatulence, diarrhoea, loss of appetite or any other adverse report were noted at each visit. All parameters under study were screened at 6-8 monthly interval and again at the end of the study period. Treatment failure patients were planned to be treated with either thiazolidinediones or nocturnal intermediate acting insulin or a combination of short acting and intermediate acting insulin in addition to combined glimeperide and metformin therapy. Any episode of hypoglycaemia was planned to be managed by instant administration of oral glucose.

Group A patients were ultimately administered 25mg of Miglitol thrice daily while group B patients were given 50mg of Acarbose thrice daily to attain the targeted PPBG level.

The study period was terminated at the completion of 18 months for each patient and the periodically collected data were statistically analyzed for significance.

Statistical Methods : All statistical analysis were performed by using SPSS software , version 16 and data have been summarised as counts and percentages. Paired proportions have been compared using Paired t test and the p value of < 0.05 was considered statistically significant .

## RESULTS

Comparison of collected data regarding PPBS and HbA1C of patients of either group at first visit, to that obtained at last follow up shows the following results :

Miglitol as add-on drug titrated to a maximum dose of 25mg thrice daily over 18 month period produced a mean reduction of PPBS of  $34.12 \pm 4.89\%$  (**Table -1**). Acarbose as add-on drug titrated to a maximum dose of 50mg thrice daily over 18 month period produced a mean reduction of PPBS of  $30.61 \pm 5.86\%$  (**Table -2**).

Since the sample size in each group were  $< 30$ , t-test was used to analyze the differences between the two readings. The **p value** obtained was **0.01293**, which is less than 0.05. This shows that the efficacy of Miglitol is significantly better than Acarbose (**Figure 1**).

Comparison of the HbA<sub>1c</sub> readings of patients at the initial phase of study to the data derived at the end of study shows that the mean reduction in HbA<sub>1c</sub> with Miglitol was  $0.58 \pm 0.05$  g% (**Table 3**) while that of Acarbose was  $0.47 \pm 0.09$  g% (**Table 4**). The p value obtained using t-test was **0.0000008**, hence highly significant. This re-emphasizes that the efficacy of Miglitol is significantly better than Acarbose (**Figure 2**).

## DISCUSSION

Results of PPBS of both groups when compared from initial to subsequent and final visits were found to be better with Miglitol than Acarbose (**Table 1 and 2**). As most patients complained of diarrhoea following 50mg of Miglitol, the dose was limited to 25mg thrice daily. Patient tolerability with 50mg of Acarbose was better except for flatulence. As dose response with Acarbose was less compared to Miglitol, the dose of Acarbose was increased to a maximum of 50mg thrice daily. LFT showed slight increase with Acarbose after 6 months of therapy but both blood urea, creatinine as well as blood AST, ALT levels were within limits with Miglitol. The main adverse effect following Miglitol therapy was diarrhoea, while both flatulence and diarrhoea were noted with Acarbose. In most patients diarrhoea subsided with continuation of therapy. There was no reported incidence of weight gain, rather most patients under therapy reported about 2-5kg weight loss over the 18 months study period. A few probable symptoms of hypoglycemia was reported in two patients with 50mg Miglitol but was not confirmed biochemically. The symptoms subsided on taking oral glucose tablets as advised.

As per results of the study, it can be stated that alpha-glucosidase inhibitors are safe and efficacious drugs as add on therapy in Type 2 diabetes mellitus patients already on combination therapy of sulphonylurea and metformin. Both  $\alpha$ -glucosidase inhibitors, Acarbose and Miglitol are effective in lowering PPBS as well as HbA<sub>1c</sub>, but efficacy and tolerability of Miglitol was proven to be better than Acarbose.

Previous study by Rybka J. et. al. shows that compared to placebo, Acarbose decreases HbA<sub>1c</sub> by 0.7% and Miglitol by 0.68%<sup>4</sup> whereas in our study we find Miglitol has decreased HbA<sub>1c</sub> by 0.58% (**Table 3**) while Acarbose by 0.48% (**Table 4**) as minimum dose add on therapy to Glimeperide 4mg and Metformin 2g. With acarbose dosages higher than 50 mg thrice daily, the effect on Glycosylated Hb remains the

same, but the occurrence of side effects increases<sup>4</sup>. Similar response was noted on this study.

Clinical trials with Miglitol, in 50-100mg three times daily in type 2 diabetes patients has been found to produce consistent improvement in glycaemic control over a 6-12 month period. Miglitol may prove particularly beneficial in elderly patients and those with hepatic impairment or mild to moderate renal impairment or in whom other oral antidiabetic agents are contraindicated<sup>9</sup>. Miglitol is a 1-deoxynojirmycin derivative, structurally resembling a glucose molecule which reversibly inhibits intestinal  $\alpha$  glucosidase enzymes responsible for the digestion of carbohydrates to absorbable monosaccharides<sup>10</sup>. In a previous study, Miglitol in combination with metformin used in Type 2 Diabetes patients produced better glycaemic control in respect to fasting and postprandial blood glucose as well as HbA<sub>1c</sub> levels<sup>10</sup>. In this study dose of Miglitol kept to minimum was found to be effective when given in addition to Metformin and Sulphonylurea. Hypoglycaemic episodes were not reported during clinical studies with Miglitol at therapeutic doses but miglitol produces a significant depression of post-peak blood glucose compared to placebo or acarbose<sup>11,12,13</sup>. Acarbose a tetra-saccharide compound is only minimally absorbed after oral administration and is associated with a relatively high incidence of gastrointestinal symptoms secondary to fermentation of unabsorbed carbohydrates<sup>14</sup>. Miglitol, a 1-desoxynojirmycin derivative, structurally related to glucose and considered second generation  $\alpha$ -glucosidase inhibitor, is well absorbed from the small intestine<sup>13,15</sup>. It was speculated that absorbable  $\alpha$ -glucosidase inhibitors such as miglitol would have a lower propensity for gastrointestinal adverse effects<sup>16</sup>. Absorbable  $\alpha$  glucosidase inhibitors can exert an inhibitory effect on non-intestinal  $\alpha$  glucosidases present in various cell types but there is little risk of inducing unwanted side-effects when Miglitol is administered at an oral dose of 1mg/Kg body weight<sup>17</sup>. Miglitol effectively enhances postprandial GLP-1 release and suppresses plasma GIP secretion and significantly lowers feelings of hunger, inducing sensations of satiety in obese-type 2 diabetic patients<sup>18</sup>. Alpha glucosidase inhibitors must be taken with meals, in which carbohydrates make up a minimum of 40% of the diet, for these agents to be effective<sup>19</sup>. India is a agriculture based country where maximum people have rice/ wheat as their staple diet. Long term administration of  $\alpha$ -glucosidase inhibitors did not induce any appreciable degree of carbohydrate malabsorption<sup>20</sup>. One drawback of acarbose treatment is an association with hepatotoxicity<sup>21</sup>, though it was not observed in this study, perhaps due to the minimum dose used.

## CONCLUSION

Type 2 Diabetes forms the greatest burden and holds a significant share of the Diabetic load in India. India being an

agriculture based country, cereals in the form of carbohydrates form the staple diet of most Indians. Thus  $\alpha$  glucosidase inhibitors are sure to play an important role as an add on therapy when first line drugs like sulphonylurea and biguanides fail to control the hyperglycaemia in these type of patients.

As these drugs have minimum adverse effects, with more or less similar efficacy, they can be included in the oral antidiabetic therapy as second line or add on drugs to control the PPBS in majority of Indians who consume a carbohydrate based diet.

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**Table 1 : Comparative data of Post Prandial Blood Sugar levels before and after Miglitol add on therapy (n=25)**

Patients' Serial No.	PPBS at first visit	PPBS at the end of study	Reduction	% Reduction
1	228	140	88	38.60%
2	248	157	91	36.69%
3	178	122	56	31.46%
4	213	114	99	46.48%
5	181	127	54	29.83%
6	272	180	92	33.82%
7	204	135	69	33.82%
8	190	117	73	38.42%
9	195	133	62	31.79%
10	223	159	64	28.70%
11	230	140	90	39.13%
12	204	150	54	26.47%
13	216	133	83	38.43%
14	245	151	94	38.37%
15	240	155	85	35.42%
16	234	158	76	32.48%
17	207	124	83	40.10%
18	226	136	90	39.82%
19	186	127	59	31.72%
20	214	145	69	32.24%
21	212	147	65	30.66%
22	168	114	54	32.14%
23	188	131	57	30.32%
24	182	135	47	25.82%
25	162	113	49	30.25%
Mean % reduction			34.12%	
Standard deviation			±4.89%	

**Table 2: Comparative data of Post Prandial Blood Sugar levels before and after Acarbose add on therapy (n=25):**

Patient Serial No.	PPBS at first visit	PPBS at the end of study	Reduction	% Reduction
1	190	136	54	28.42%
2	187	123	64	34.22%
3	194	130	64	32.99%
4	235	174	61	25.96%
5	215	121	94	43.72%
6	181	135	46	25.41%
7	215	152	63	29.30%
8	228	130	98	42.98%
9	220	142	78	35.45%

10	184	138	46	25.00%
11	189	142	47	24.87%
12	226	160	66	29.20%
13	203	148	55	27.09%
14	224	151	73	32.59%
15	192	138	54	28.13%
16	200	152	48	24.00%
17	186	136	50	26.88%
18	193	141	52	26.94%
19	190	134	56	29.47%
20	205	142	63	30.73%
21	213	129	84	39.44%
22	240	148	92	38.33%
23	196	152	44	22.45%
24	188	138	50	26.60%
25	194	126	68	35.05%
Mean % reduction			30.61%	
Standard deviation			±5.86%	

Degrees of freedom df = 48 , P value = 0.01294  
 Since p value is less than 0.05, Miglitol has performed significantly better

**Table 3: Comparative data of HbA1C (in gm %) levels before and after Miglitol add on therapy (n=25) :**

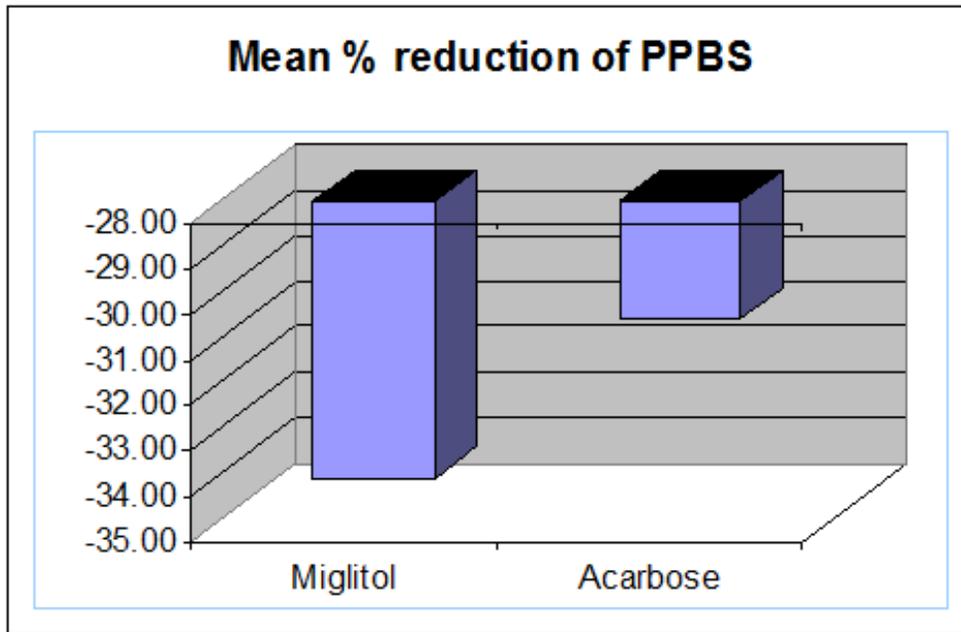
Patient Serial No	HbA1c at first visit	HbA1c at the end of study	Reduction
1	7.7	7.0	0.7
2	7.2	6.6	0.6
3	7.6	7.0	0.6
4	6.9	6.3	0.6
5	7.5	6.9	0.6
6	7.0	6.4	0.6
7	6.9	6.4	0.5
8	7.0	6.4	0.6
9	7.1	6.5	0.6
10	7.7	7.0	0.7
11	7.6	7.0	0.6
12	7.1	6.5	0.6
13	6.9	6.4	0.5
14	7.1	6.6	0.5
15	7.4	6.8	0.6
16	7.0	6.4	0.6
17	7.0	6.5	0.5

18	7.4	6.8	0.6
19	7.3	6.7	0.6
20	7.6	7.0	0.6
21	7.4	6.8	0.6
22	7.0	6.5	0.5
23	6.9	6.4	0.5
24	7.2	6.6	0.6
25	7.4	6.8	0.6
<b>Mean Reduction</b>		<b>0.584</b>	
<b>Standard Deviation</b>		<b>0.0553775</b>	

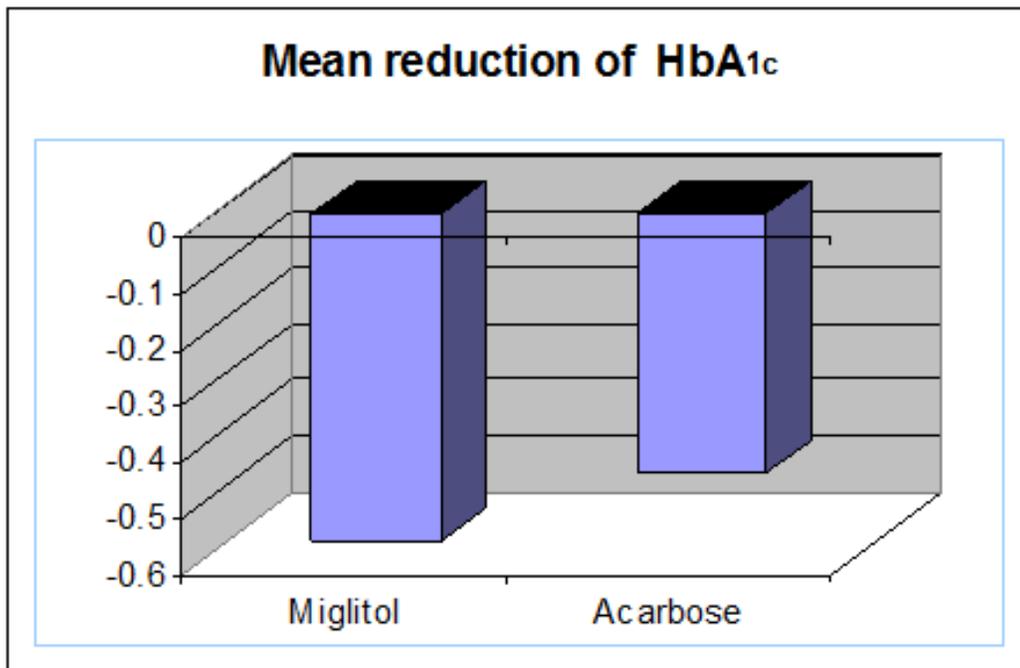
**Table 4: Comparative data of HbA1C (in gm %) levels before and after Acarbose add on therapy (n=25) :**

Patient Serial No	HbA1c at first visit	HbA1c at the end of study	Reduction
1	7.3	6.8	0.5
2	7.4	6.9	0.5
3	6.9	6.5	0.4
4	7.3	6.9	0.4
5	6.9	6.6	0.3
6	7.4	6.9	0.5
7	7.3	6.7	0.6
8	7.0	6.7	0.3
9	7.1	6.8	0.3
10	7.3	6.8	0.5
11	7.4	6.9	0.5
12	7.2	6.8	0.4
13	7.5	6.9	0.6
14	7.5	6.9	0.6
15	7.5	6.9	0.6
16	7.3	6.8	0.5
17	7.2	6.7	0.5
18	7.3	6.9	0.4
19	6.9	6.5	0.4
20	7.5	7.0	0.5
21	6.9	6.5	0.4
22	7.4	6.9	0.5
23	7.1	6.6	0.5
24	7.4	6.9	0.5
25	7.1	6.7	0.4
<b>Mean reduction</b>		<b>0.464</b>	
<b>Standard Deviation</b>		<b>± 0.09</b>	

Degrees of freedom df = 48 , p value = 0.00000871857  
 Since p value is less than 0.05, Miglitol has performed significantly better



**Figure 1:** Comparative data showing mean percentage reduction of Post Prandial Blood Sugar between Miglitol and acarbose treatment groups (n=25)



**Figure 2:** Comparative data showing mean reduction of HbA1c between Miglitol and acarbose treatment groups (n=25)