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COMPARATIVE INVESTIGATION OF ANTIDIABETIC ACTIVITY OF ACARBOSE, MIGLITOL AND SALACIA OBLONGA IN PATIENTS OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

Acarbose, Miglitol and Voglibose are the marketed α -glucosidase inhibitor used to reduce post prandial glucose level in the patients of type 2 diabetes mellitus. Increased post prandial blood is cause of number of disease in such patients. *Salacia Oblonga* and *Salacia Reticulata* are plants native to India and Sri Lanka these are widely used for thousands of years in Ayurvedic medicine for the oral treatment of diabetes, Attenuation of postprandial glycemia is hypothesized to reduce the risk of progression from impaired glucose tolerance to diabetes. It is also thought to reduce the number of complications associated with diabetes. A clinical trial conducted to assess the comparison of outcome of marketed drugs and with *salacia oblonga*, found significant effect on weight and HbA1C value of patients of Type II DM.

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INTRODUCTION

Carbohydrates must be digested into monosaccharides before they are absorbed from the intestinal tract. Starch is obviously such a case. Even disaccharides such as sucrose, maltose and lactose are not absorbed until they are degraded by disaccharidase into monosaccharides such as glucose and fructose [1]. Alpha-glucosidase inhibitors are used in the treatment of type 2 diabetes mellitus. They act by a reversible inhibition of alpha-glucosidase, an enzyme present in the brush border of the small intestine. Alpha glucosidase inhibitors delay absorption of complex carbohydrates and thus inhibit postprandial glucose peaks thereby leading to decreased postprandial insulin levels. Currently, three alpha-glucosidase inhibitors exist: acarbose, miglitol and voglibose. Of those, acarbose is by far the most prescribed drug [2, 3, 4]. Because of its lowering effect on the postprandial elevation of insulin levels, a beneficial effect on body weight is to be expected. Further, a positive effect on hypertriglyceridaemia has been reported. Abdominal discomfort like flatulence, diarrhoea and stomachache are the most frequently occurring adverse effects of alpha-glucosidase inhibitors. Because of their specific working mechanism hypoglycaemic adverse events do not occur. They do not increase insulin output potentially leading to hypoglycaemia [2]. Accumulating evidence shows that excessive fluctuations in post meal blood glucose levels (postprandial hyperglycemia) have adverse consequences for diabetes related morbidity and mortality. It is now apparent that postprandial hyperglycemia plays a central role in the decline from impaired glucose tolerance (IGT) to overt diabetes and in the development and progression of diabetes complications, particularly cardiovascular disease (CVD), good glycemic control reduces the risk of vascular complications [5, 6] and prevention of postprandial hyperglycemia decreases the risk for both type 2 diabetes and CVD in individuals with IGT [7]. Consequently, postprandial glucose control in conjunction with normalization of hemoglobin HbA1c and fasting plasma glucose levels in those with manifest diabetes should be a primary goal in the prevention and management of type 2 diabetes.

Prevalence of Diabetes Mellitus in India [8]:

According to the latest IDF estimates, 50.8 million people in India diagnosed with diabetes in 2010 and the figure will increase to approximately 75 million in 2025 and almost 80 million by 2030 [9]. Phase one results of the Indian Council of Medical Research India Diabetes (ICMR-INDIAB) study have provided data from three States and one Union Territory, representing nearly 18.1 per cent of the nation's population. When extrapolated from these four units, the conclusion is 62.4 million people live with diabetes in India, and 77.2 million people are on the threshold, with pre-diabetes [10]. In diabetes, the postprandial phase is characterized by a rapid and large increase in blood glucose levels, which is called postprandial hyperglycemia or "hyperglycemic spikes" [11, 12, 13]. In modern medicine, the efficacy of an intervention should be investigated in well-designed randomized trials. Results from the trials should be collected in a high-quality systematic review, if possible with a meta-analysis. And finally, the evidence should have its repercussions on practice guidelines.

MATERIALS AND METHODS:

Duration of study:

The expected duration for participation of each subject enrolled in the study was 6 months. **Methodology:**

Study Site:

Government Medical College and Hospital Aurangabad, Deogiri Diabetic Research Center Aurangabad.

Study Design:

This is open label; parallel study.

Study Period:

The study was conducted for a period of six months from June 2010 to February 2011

Study criteria:

Patients with eligible for study having prediabetes, HbA1c value between 5.7 to 7.5 and FBS more than 110 and PBS more than 140 are enrolled in study.

Study Procedure:

Study protocol approved by the Ethical committee of Govt. Medical College and Hospital, Aurangabad. One hundred and fifty (n=150) Type-2 diabetes patients were enrolled in the study. These patients divided into three groups and each group enrolled fifty (50) patients. Patients were explained about the study pattern and related hazards. Informed written consent was obtained from the patients. A detailed clinical history will be taken and clinical examination will be performed. Those included will undergo all baseline investigations like complete blood count, liver function tests, kidney function tests, blood sugar level, fundoscopy and Glycated Hb, triglyceride levels and TSH at the start of the study and at the end of the study. Enrolled patients will be divided into three groups of 50 each according to random number table. Each patient in respective group will be provided free samples for fifteen days and asked to visit the diabetic clinic for follow up and for collection of drugs. At each follow up visit, patients will be assessed for glycemic control (blood sugar level) once in a month (4 weekly), history pertaining to adverse drug effect will be asked. All patients will be given advice about diet and exercise. The study population will not allow taking antidiabetic drugs other than study drugs.

Table No. 01. Patients Group (150 Patients).

Group I	Acarbose
Group II	Miglitol
Group III	Salacia Oblonga

Efficacy Measures:

1. Change in Fasting blood glucose level from baseline to end of study (6 Months)
2. Change in Post meal blood glucose level from baseline to end of study (6 Months)
3. Change in Glycosylated haemoglobin (HbA1C) from baseline to end of study (6 Months).
4. Change in weight from baseline to end of study (6 Months)

Collection of Blood Samples:

Patients were asked to come fasting in diabetic clinic, 2 ml of venous blood sample were collected in fluoride bulb to estimate the fasting blood sugar levels, followed by assessment of Postprandial blood sugar values after 2 hours. **Sample Analysis:** Estimation of blood Glucose Level and Glycated Hb

Blood Glucose estimation:

Trinder's Method

Blood HbA1C estimation:

NYCORD reader.

Ethical Committee Approval:

Intuitional Ethical Committee Clearance was obtained from the Ethical Committee of Government Medical College and Hospital Aurangabad.

Dropouts:

07 patients left study from acarbose group before completion of study.

Adverse Drug Reaction:

In some patients from acarbose and miglitol group GI disturbances and epigastric distress observed.

Statistical Analysis:

For comparing the effect of Acarbose, Miglitol with Salacia oblonga on blood sugar level and HbA1c before and after therapy, statistical analysis was done by descriptive statistics as mean, SD, percentage, proportions etc. Data were presented in the form of Tables and graphs. Student's Paired and Unpaired „t“ tests were applied to observe performance before and after stage, and comparisons of all groups under study. The probability values were considered as (p, 0.05) and (p, 0.01). At p<0.05 results were considered as significant and p<0.01, considered as highly significant. Two ways ANOVA were performed for repeated measures and Tukey– Kramer test (F test) were applied to analyze the group's data. Statistical analysis software namely SYSTAT version 12 by Cranes Software, Bangalore (a licensed copy) were used to analyze the data in the study.

Informed Consent:

Patients willing to participate and eligible in the view of investigator were given the Patient Information Sheet in his/her vernacular language and all study related tests and procedures were explained to him/her in simple yet detailed manner. After imparting sufficient information, if the patient desired to be a part of the study then his consent (signature or thumb impression) was taken in the informed consent form as in Appendix. The informed consent form was agreed by IRB/IERC

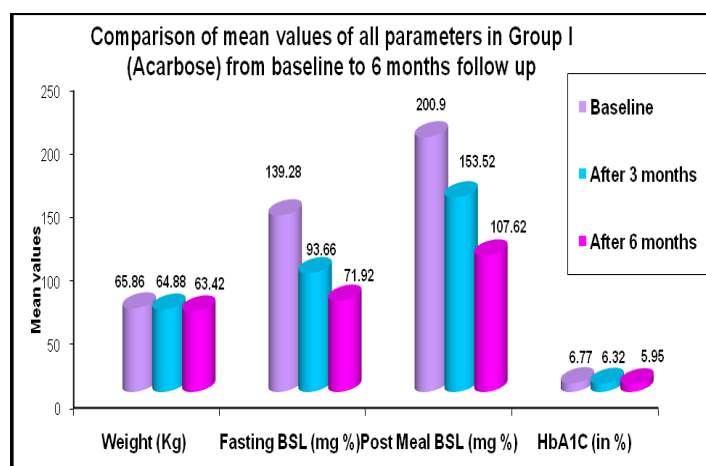
RESULT AND DISCUSSION

Each group enrolled 50 patients and Gorup I patient treated with Acarbose 50 mg tid alone Student's Paired „t“ test the average values of Weight, Fasting BSL, Post meal BSL and HbA1C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in group I (Acarbose) (p<0.01).

Distribution of mean and SD values of all parameters in Group I (Acarbose) from baseline to 6 months follow up:

Table No: 02.

Parameters	Group I (Acarbose) n=50		
	Baseline	After 3 months	After 6 months
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Weight (Kg)	65.86 $\pm$ 10.33	64.88 $\pm$ 9.72	63.42 $\pm$ 9.49
Fasting BSL (gm %)	139.28 $\pm$ 10.57	93.66 $\pm$ 9.67	71.92 $\pm$ 8.99
Post Meal BSL (gm %)	200.9 $\pm$ 20.24	153.52 $\pm$ 20.92	107.62 $\pm$ 16.96
HbA1C (in %)	6.77 $\pm$ 0.73	6.32 $\pm$ 0.73	5.95 $\pm$ 0.71



Graph No. 01: Comparison of Mean values of all parameters in Group I (Acarbose) from baseline to 6 months follow up.

Table No. 03: ANOVA Test for Group I (Acarbose).

Source of variation	Degrees of freedom (d.f.)	Sum of squares	Mean square
Treatment (between columns)	11	2074801	188618
Individual (between rows)	49	25928	529.14
Random (residual)	539	58064	107.73
Total	599	2158793	

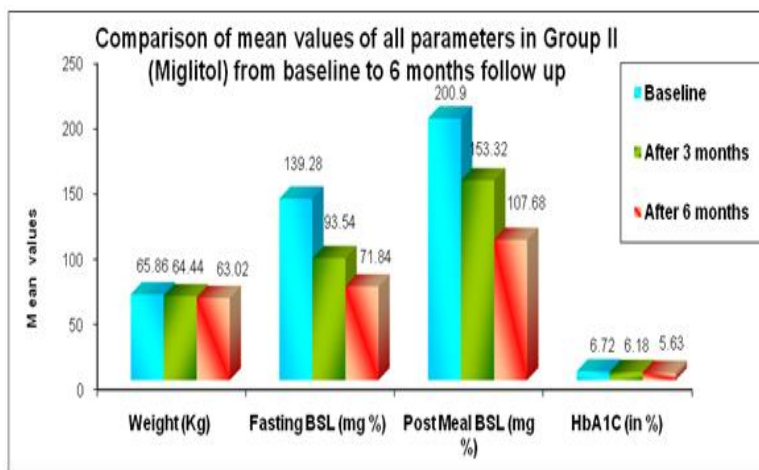
Value of "F" = 1750.9, $p < 0.001$, highly significant.

By applying Tukey-Kramer Multiple Comparison Test there is extremely highly significant difference between mean values of Weight, Fasting BSL, Post meal BSL and HbA1C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in group I (**Acarbose**) ($p < 0.01$)

Table No. 04: Distribution of mean and SD values of all parameters in Group II (Miglitol) from baseline to 6 months follow up.

Parameters	Group II (Miglitol) n=50		
	Baseline	After 3 months	After 6 months
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Weight (Kg)	65.86 $\pm$ 10.33	64.44 $\pm$ 9.95	63.02 $\pm$ 9.69
Fasting BSL (gm %)	139.28 $\pm$ 10.57	93.54 $\pm$ 9.69	71.84 $\pm$ 9.03
Post Meal BSL (gm %)	200.9 $\pm$ 20.24	153.32 $\pm$ 21.0	107.68 $\pm$ 16.92
HbA1C (in %)	6.72 $\pm$ 0.68	6.18 $\pm$ 0.65	5.63 $\pm$ 0.64

By applying Student's Paired 't' test the average values of Weight, Fasting BSL, Post meal BSL and HbA1C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in group II (Miglitol) ($p < 0.01$).



Graph No. 2: Comparison of Mean values of all parameters in Group II (Miglitol) from baseline to 6 months follow up.

Table No. 05: ANOVA Test for Group II (Miglitol).

Source of variation	Degrees of freedom (d.f.)	Sum of squares	Mean square
Treatment (between columns)	11	2078777	188980
Individual (between rows)	49	26652	543.92
Random (residual)	539	57875	107.38
Total	599	2163304	

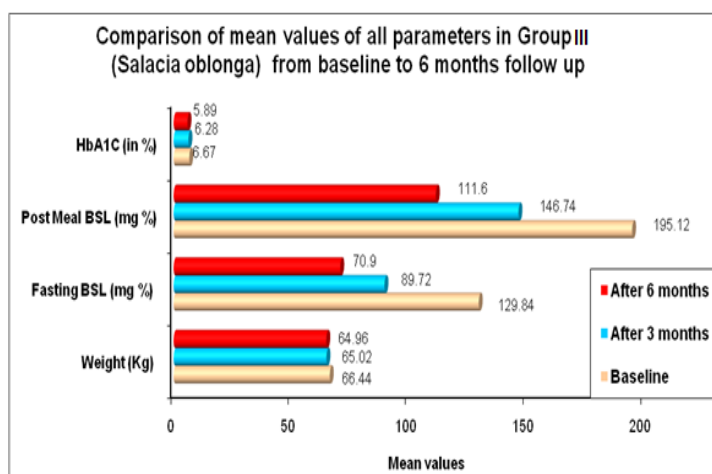
Value of “F” = 1760, $p < 0.001$, highly significant

By applying Tukey-Kramer Multiple Comparison Test there is extremely highly significant difference between mean values of Weight, Fasting BSL, Post meal BSL and HbA1C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in group II (Miglitol) ($p < 0.01$)

Table No. 06: Distribution of mean and SD values of all parameters in Group VII (*Salacia oblonga*) from baseline to 6 months follow up.

Parameters	Group III (<i>Salacia oblonga</i>) n=50		
	Baseline	After 3 months	After 6 months
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Weight (Kg)	66.44 $\pm$ 8.82	65.02 $\pm$ 8.32	64.96 $\pm$ 9.60
Fasting BSL (gm %)	129.84 $\pm$ 19.98	89.72 $\pm$ 12.99	70.90 $\pm$ 8.39
Post Meal BSL (gm %)	195.12 $\pm$ 22.53	146.74 $\pm$ 22.65	111.6 $\pm$ 18.6
HbA1C (in %)	6.67 $\pm$ 0.65	6.28 $\pm$ 0.64	5.89 $\pm$ 0.71

By applying Student’s Paired ‘t’ test the average values of Weight, Fasting BSL, Post meal BSL and HbA1C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in Group VII (*Salacia oblonga*) ($p < 0.01$).



Graph No. 03: Comparison of Mean values of all parameters in Group VII (*Salacia oblonga*) from baseline to 6 months follow up.

Table No. 07: ANOVA Test for Group III (*Salacia oblonga*).

Source of variation	Degrees of freedom (d.f.)	Sum of squares	Mean square
Treatment (between columns)	11	1916246	174204
Individual (between rows)	49	35997	734.64
Random (residual)	539	73979	137.25
Total	599	2026222	

Value of “F” = 1269.20, $p < 0.001$, highly significant

By applying Tukey-Kramer Multiple Comparison Test there is extremely highly significant difference between mean values of Weight, Fasting BSL, Post meal BSL and HbA₁C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in Group VII (*Salacia oblonga*) ($p < 0.01$)

Table No. 08: Percentage (%) decrease from baseline to 6 months for all parameters in all groups under study.

Groups	Percentage (%) decrease from baseline to 6 months			
	Weight	Fasting BSL	Post meal BSL	HbA ₁ C
Group I (Acarbose)	3.70	48.36	46.43	12.11
Group II (Miglitol)	4.31	48.40	46.40	16.22
Group VII (<i>Salacia Oblonga</i>)	2.23	45.39	42.80	11.69

DISCUSSION

The type -2 diabetes mellitus (DM) is a most common chronic disease which accompanies the patient throughout the life. Since type-2 diabetes mellitus is progressive disease, its natural course may lead to late complications which clearly restrict the life span and quality of life of patient. The cost of treating complications is also high therefore early diagnosis and adequate treatment is of critical significance for type-2 diabetes patient [14]. Accumulating evidence shows that excessive fluctuations in post meal blood glucose levels (postprandial hyperglycemia) have adverse consequences for diabetes related morbidity and mortality.

The present study investigated the effects of acarbose, miglitol and *Salacia oblonga* on lowering of FBS, PFBS, HbA1C, and weight of patient.

The postprandial lowering of blood glucose by alpha-glucosidase inhibitors such as miglitol and acarbose after a starch load is well established. The mechanism of action is the inhibition of the last step in carbohydrate digestion, namely the conversion of disaccharide to monosaccharide (glucose) and a consequent decrease in the rate of entry of glucose into the systemic circulation.

Group I treated with acarbose alone (Table No. 01) shows distribution of mean and SD values of weight, Fasting BSL, Post meal BSL, and HbA₁C parameters in group I from baseline to 6 months follow up. In present study from the table No.01, it is observed that average weight falls down from 65.86 kg at baseline to 63.42 kg at 6 months follow up. Similarly, fasting BSL falls down from 200.9 mg% at baseline to 71.92 mg% at 6 months follow up i.e. 48.36%.

In this study Post meal BSL is also fall down from 200.9 mg% at baseline to 107.62 mg% (-93.28) at 6 months follow up i.e. 46.43%

The Group I treated with acarbose alone the HbA₁C falls down from baseline i.e. 6.77% to 5.95% at 6 months follows up, a significant reduction in glycosylated hemoglobin 12.11% is obtained.

Group II treated with Miglitol alone (Table No. 04) shows distribution of mean and SD values of weight, Fasting BSL, Post meal BSL, and HbA₁C parameters in group II from baseline to 6 months follow up. Miglitol is the first pseudo monosaccharide a-glucosidase inhibitor derived from 1-deoxynojirimycin and is structurally a glucose analogue [15, 16] and efficacy in monotherapy too [17]. It is observed that average weight falls down from 65.86 kg to 63.02 kg at 6 months follow up net drop by 2.84 kg i. e. 4.31%. The fasting blood sugar level in Group II treated with Miglitol dropped by 139.28±10.57 to 71.84±9.03 i.e. 48.40%. The decrease in the post meal blood sugar level in this study is 200.9±20.24 to 107.68±16.92 i. e. 46.40%. Group II HbA₁c value in this study is dropped by 6.72±0.68 to 5.63±0.64 net drop by 1.09 i.e. 16.22%.

Group III treated with *Salacia oblonga* 500 mg tid Table No.06. Shows distribution of mean and SD values of weight, Fasting BSL, Post meal BSL, and HbA₁C parameters in group VII from baseline to 6 months follow up. In present study from the table No. 06. It is observed that average weight falls down from 66.44 kg at baseline to 64.94 kg i.e. 1.50 kg at 6 months follow up. The fasting BSL falls down from 129.84 mg% at baseline to 70.90 mg% at 6 months follow up. Post meal BSL is also fall down from 195.12 mg% at baseline to 111.6 mg% at 6 months follow up. The HbA₁c value reduced from 6.67 to 5.89 there is noticeable 11.69% reduction. By applying Student's Paired 't' test the average values of Weight, Fasting BSL, Post meal BSL and HbA₁C are highly significantly decreased from base line to after 6 months in patients with Type – 2 Diabetic Mellitus in Group VII (*Salacia oblonga*) (p<0.01)

In this study the percentage decrease of weight, fasting blood sugar level, post meal blood sugar level and HbA₁c in three group, we can conclude that the Group II treated with Miglitol has significant effect on weight loss. It reduces the weight by 4.31% as well the fasting blood sugar level by 48.40% and more important the HbA₁c value by 16.22%.

The group I treated with Acarbose shows significant decrease in post meal blood sugar level by 46.43% which is comparative more than other groups.

It is vivid that the Miglitol is important drugs for the patients whose weight, fasting and HbA₁c level to be controlled.

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