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EARLY AGGRESSIVE TREATMENT: METFORMIN-VOGLIBOSE COMBINATION THERAPY VS METFORMIN MONOTHERAPY IN TYPE 2 DIABETES MELLITUS PATIENT.

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ABSTRACT

Diabetes has rapidly gained the status of being a pandemic. Adequate treatment of diabetes mellitus is very challenging. Numbers of drugs, with different mechanism of action, catering the needs of diverse patient profile are being marketed. Nowadays early aggressive treatment with combination therapy is advocated for achieving tight glycemic controls, keeping a check on hypoglycaemia. Therefore present study was designed to compare effectiveness of metformin-voglibose combination regime with metformin monotherapy in newly diagnosed T2DM. **Method-** The present study was designed as open, parallel and randomized comparison of effectiveness of metformin-voglibose with metformin alone over a period of 24 weeks in newly diagnosed T2DM patients attending Internal medicine OPD, Rajindra Hospital Patiala. 80 patients were randomly allocated into two treatment group after verifying for inclusion and exclusion criteria and obtaining written informed consent. Maximum dose of metformin given was 2.5 g/d and that of voglibose was 0.9mg/d.FBS and PPBS were done at baseline 4th week, 12th week and 24th week. HbA_{1C} was monitored at baseline 12th week and 24th week. **Results-** At the end of 24 weeks metformin monotherapy reduce HbA_{1C} by 1.56±0.59%, FBS by 34.12±16.70 mg/dL and PPBS was reduced by 78.37±32.2 mg/dL. Combination therapy reduced HbA_{1C} by 1.73±0.56, FBS by 41.60±27.38 mg/dL and PPBS was reduced by

94.22±19.80 mg/dL. **Conclusion-** Combination therapy showed greater reduction in PPBS as compared to Metformin monotherapy.

KEYWORDS: Diabetes mellitus, Voglibose, Metformin, Postprandial hyperglycaemia, early aggressive treatment.

INTRODUCTION

The total economic cost of diabetes in 2012 was $245 billion in United states, as compared to $174 billion in 2007. This increment of nearly 41% in expenditure of the disease reflects increasing burden that the disease imposes on the society.[1]

The therapeutic understanding to treat DM has expanded considerably in recent years. There are number of drugs now available that cater to the needs of diverse patient profile.[2,3]

Metformin is well known not only for its anti-hyperglycemic but also for its other beneficial effects on endothelial dysfunction, hemostasis oxidative stress, insulin resistance, lipid profiles and fat redistribution.[4] How ever in last decade there were several reports that have documented that metformin alone does not affect insulin secretion and its effects on overall glycemic control are achieved mainly by the reduction of fasting plasma glucose and not post-prandial glucose levels.[5,6]

It is now recognized that postprandial hyperglycemia is an independent risk factor for macro-vascular complications.[7] During the management of diabetic patient controlling elevated PPBS is most challenging. It gets complicated by the fact that monitoring of PPBS is widely ignored in clinical practices, whereas FBS and HbA_{1C} are routinely monitored.[8] Therefore to provide adequate management of type-2 diabetes mellitus one should also do regular monitoring of PPBS along with FBS and HbA_{1c}.[9] It is now considered that control of postprandial hyperglycaemia is essential for achieving HbA_{1C} goals of ≤6.5%.[10] The landmark UKPDS showed that every reduction of 1% HbA_{1c} reduced the risk of all microvascular and macrovascular chronic complications.[11] Individual patient profile, one can choose an appropriate combination regime of two insulin sensitizers, or one sensitizer and secretagogue, or one sensitizer and one α-glucosidase inhibitor to initiate therapy in patients of T2DM.[12] Drugs that target specifically PPBS include alpha glucosidase inhibitors, glinides and pre-meal insulin. Alpha glucosidase inhibitors e.g. Acarbose are most

commonly used drugs for controlling post prandial hyperglycaemia. Unlike other drugs they are euglycemic.[13,14]

Surprisingly there is limited number of studies available about the effectiveness of newer α-glucosidase inhibitor voglibose as add on therapy with metformin to achieve targeted glycemic control . So this study has been designed to compare effectiveness of metformin alone with voglibsoe and metformin combination type 2 diabetes mellitus patients attending medicine OPD at Rajindra hospital Patiala.

MATERIAL AND METHOD

This was a prospective, randomized, open label, parallel group study done in collaboration with the Department of Medicine, Rajindra Hospital, Patiala. Patients diagnosed with type-2 diabetes mellitus were enrolled in the study as per inclusion and exclusion criteria.

INCLUSION CRITERIA

1. Newly diagnosed cases of type- 2 diabetes mellitus as per WHO criteria.
2. Patients above 18 years of age.
3. Patient of either sex.
4. Patient with HbA_{1c} level of 7.5-10% at the time of recruitment.
5. Patient willing to give written informed consent.

EXCLUSION CRITERIA

1. Patients with type-1 diabetes mellitus.
2. HbA_{1c} level >10 % at the time of recruitment.
3. Pregnant and lactating female patients.
4. History of cardiovascular disorders.
5. History of any major gastrointestinal disorders e.g., inflammatory bowel disorder
6. Patient with history of hepatic diseases.
7. Patient with history of renal impairment.
8. History of Diabetic ketoacidosis.
9. Patient with history of lactic acidosis.
10. History of hypersensitivity or intolerance to study medication.
11. History of any other endocrinological disorders.

STUDY CONDUCT

A total of 80 patients satisfying the inclusion and exclusion criteria were enrolled for the study after obtaining the approval from institutional ethics and research review board. All patients were provided with patient information sheet in language understandable to them. Written informed consent was taken prior to participation in the present study.

At the start of the study (1st visit) demographic data was obtained along with detailed present and past medical history. Detailed physical examination was also done. The baseline investigations done included Fasting blood sugar, Post prandial blood sugar, HbA_{1c}.

Eligible patients were then randomly allocated in 1:1 ratio into 2 groups, using the block randomization technique. Patients in group 1 were given oral metformin 500 mg OD/BD. Whereas in group 2 patients were given oral metformin 500 mg OD/BD and oral voglibose 0.2/0.3 mg TDS levels. Voglibose was taken at the beginning of a major meal. Upon follow up the doses were titrated in both the study groups depending on blood glucose levels. Maximum dose of metformin was 2.5 gm/day and of voglibose was 0.9 mg/day.

The patients were instructed to come for the follow up visit at 4th week, 12th week and 24th week. During follow up at 4th week FBS and PPBS were done. Doses of the drugs were altered accordingly, if needed. During the 12th and 24th visit FBS, PPBS and HbA_{1c} were repeated. Detail records of patient's signs, symptoms and adverse effects were maintained at each visit.

EFFICACY ASSESSMENTS

The primary efficacy endpoint was a reduction in HbA_{1c} seen at 24th week. Secondary efficacy endpoints included reduction in FBS and PPBS observed at 24th week.

Statistical analysis

The results of all patients were pooled from both the group. Data was statistically analyzed using student 't' test and Chi square test. The results were finally displayed in tables and graphs. Statistical analysis was done by using SPSS 20 software.

RESULTS

80 patients of newly diagnosed type-2 diabetes mellitus were enrolled for the study and randomized into two groups of 40 patients each. The mean age in group 1 was 47.85±10.74 years and in group 2 was 53.17±11.64 years. The maximum number of patients belonged to

the age group of 41-50 years in both the groups .In group 1, 60% were female and 40% were male patients. In group 2, 57.50% were females and 42.50% were male patients. Mean height for patients in group 1 was 5.54±0.24 foot and in group 2 was a 5.49±0.22 foot. Mean weight for patients in group 1 was 75.97±13.79 kg and in group 2 was 75.02±15.12 kg. Mean BMI for patients in group 1 was 26.69±5.31 kg/m^2 and in group 2 was 26.78±5.25 kg/m^2. Both the groups were comparable at the baseline.

1) Primary end point

HbA_{1C}

The difference in mean HbA_{1c} reduction between the two groups at the end of 12 weeks was 0.02%. Statistically, which is not significant (p-value >0.05) (Table 1). At the end of 24 weeks difference in mean HbA_{1C} reduction between the two groups was 0.05%. Statistically, which is not significant (p-value >0.05) (Table 1).

2) Secondary end points

FBS

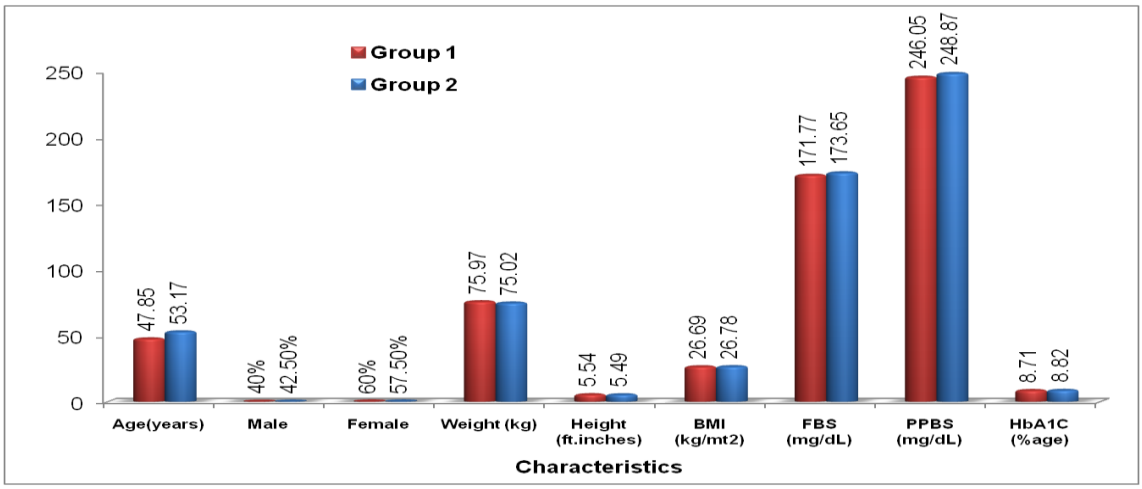
The difference in mean FBS reduction between the two groups at the end of 4th week was 1.45 mg/ dL. Statistically, which is not significant (p-value >0.05) (Table 1). The difference in mean FBS reduction between the two groups at the end of 12 weeks was 7.25 mg/dL. Statistically, which is not significant (p-value >0.05) (Table 1). At the end of 24 weeks mean difference in FBS reduction between the two groups was 5.60 mg/dL. Statistically, which is also not significant (p-value >0.05) (Table 1).

PPBS

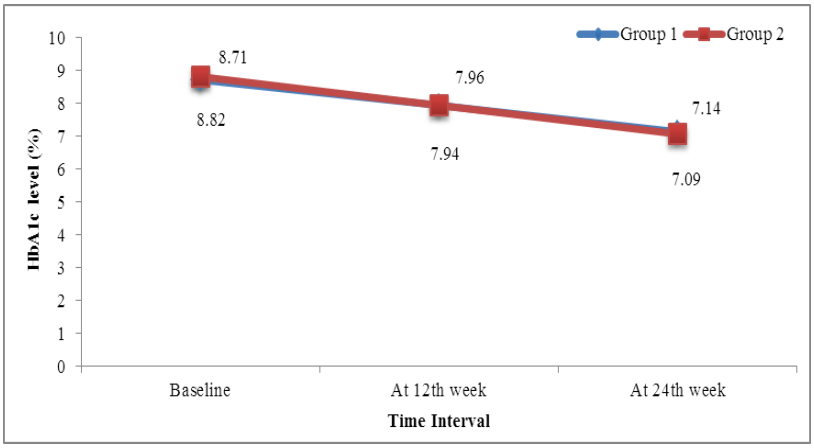
The difference in mean PPBS reduction between the two groups at the end of 4th week was 10.07mg/dL. Statistically, which is significant (p-value <0.01) (Table 1). The difference in mean PPBS reduction between the two groups at the end of 12 weeks was 12.50 mg/dL. Statistically, which is also significant (p-value <0.01) (Table 1). At the end 24 weeks mean difference in PPBS reduction between the two groups was 13.47 mg/dL. Statistically, which is highly significant (p-value < 0.001) (Table 1).

Table -1 Comparison of various efficacy parameters between both groups at various time intervals.

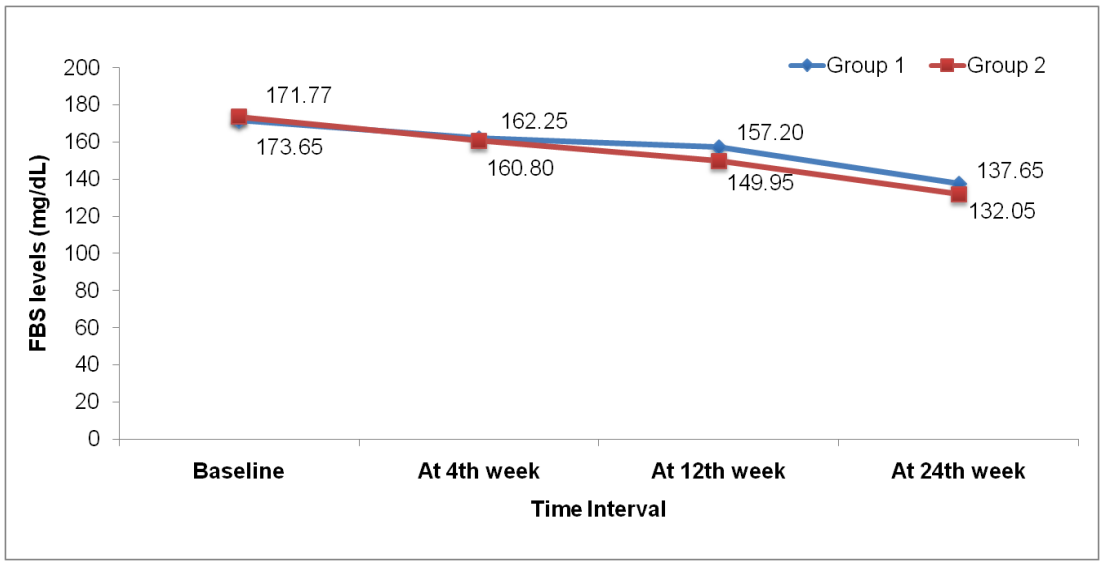
Parameter	Time Interval	Group 1	Group 2	Mean Difference	%age Change	t-value	p-value	Sig.
Hb1AC	Baseline	8.71±0.47	8.82±0.47	-0.11	-1.26	1.071	0.287	NS
	At 12th week	7.96±0.55	7.94±0.41	0.02	0.25	0.185	0.854	NS
	At 24th week	7.14±0.44	7.09±0.31	0.05	0.70	0.586	0.560	NS
FBS	Baseline	171.77±24.31	173.65±21.76	-1.87	-1.09	0.363	0.717	NS
	At 4th week	162.25±24.29	160.80±21.49	1.45	0.89	0.283	0.778	NS
	At 12th week	157.20±22.78	149.95±17.53	7.25	4.61	1.595	0.115	NS
	At 24th week	137.65±17.33	132.05±19.45	5.60	4.07	1.36	0.178	NS
PPBS	Baseline	246.05±33.71	248.87±25.73	-2.37	-0.96	0.354	0.724	NS
	At 4th week	205.07±20.17	195.00±16.12	10.07	4.91	2.468	0.016	S
	At 12th week	183.15±20.53	170.65±15.17	12.50	6.83	3.097	0.01	S
	At 24th week	168.12±22.18	154.65±15.70	13.47	8.01	3.136	0.001	HS



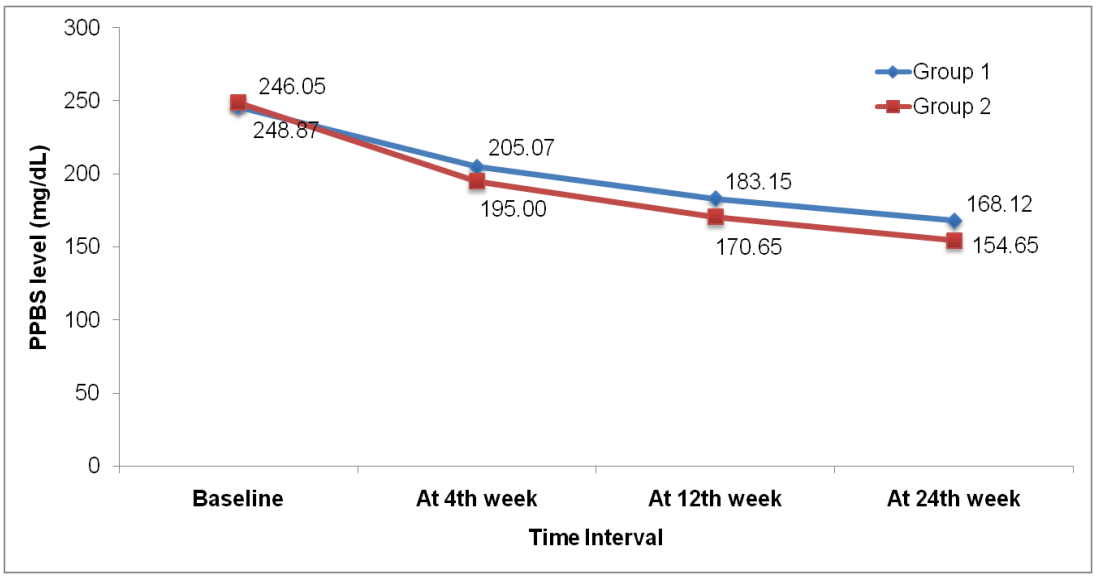
Demographic and Baseline Characteristics of the Patients in Both Groups.



Comparison of HbA1c levels (mean±sd in %) between both groups at various time intervals.



Comparison of fasting blood sugar levels (mean±sd in mg/dl) between both groups at various time intervals.



Comparison of post prandial blood sugar levels (mean±sd in mg/dl) between both groups at various time intervals.

DISCUSSION

Anti-diabetic agents are reasonably effective as monotherapy in improving glycemic control. The recent trend has been to combine agents with different modes of action early in course of therapy to produce additive effects. This additive effect provides a better glycemic control. Because of which the incidence of micro and macro vascular complications decreases. Although care has to been taken that patient does not develop hypoglycaemia because of the combination therapy.

A highly significant reduction in FBS, PPBS and HbA_{1C} were observed in both the groups at the end of 24th week of the study. Various studies have reported significant reduction in these parameters with OHAs.[15-18] However on comparison there was no significant difference in reduction of FBS and HbA_{1C} levels at the end of 24 weeks. But on comparison there was significant difference in reduction of PPBS at 4th week and 12th week and highly significant difference in reduction of PPBS at 24th week in metformin-voglibose combination therapy group. Chiasson and Naditch observed highly significant reduction in PPBS with miglitol plus metformin.[19] This could be possible be explained with use of voglibose in combination therapy group that specifically lowers postprandial blood glucose levels. Lee at al have observed favourable reduction in PPBS with the use of voglibose.[20]

CONCLUSION

Early institution of voglibose should be done in patients whose postprandial hyperglycaemia is not adequately controlled with metformin alone. The study with larger sample size and longer duration of time period is needed to further confirm the results of the present study. Although metformin and voglibose are routinely clinically prescribed yet, there are very few studies documenting the effectiveness of the metformin and voglibose combination therapy.

ABBREVIATIONS

BMI	BODY MASS INDEX
FBS	FASTING BLOOD SUGAR
HbA_{1C}	GLYCOSLATED HEMOGLOBIN
PPBS	POSTPRANDIAL BLOOD SUGAR
T2M	TYPE-2 DIABETES MELLITUS
UKPDS	UK PROSPECTIVE DIABETES STUDY
WHO	WORLD HEALTH ORGANISATION

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