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A Comparative Study of Metformin plus Sulfonylureas Versus Metforminalone for its efficacy in Type 2 Diabetes patients

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ABSTRACT: The objective of the study was to compare the efficacy of combination containing Metformin plus Sulfonylureas (MET+GLI/GLIB) and to determine whether combination of Sulfonylureas had clinically remarkable benefit over Metformin alone (MET) in patients with Type 2 Diabetes. This was a single centric, open labelled, prospective study, involving 70 Type 2 diabetes patients betweenage group of 18-75 yearsold. Data of only Type 2 diabetic patients who were prescribed eitherMetformin 500 mg,Metformin plus Glimepiride (500+2) mg and Metformin plus Glibenclamide (500+5) mg were included in the study. Efficacy was evaluated based on changes in RBS and FBS at every follow-up of one month for totally 3 months. Total 70 patients were enrolled in the study but 6 patients lost follow up in MET Group and 2 patients in MET + GLI Group. Therefore 24 patients in MET, 18 patients in MET + GLI group and 20 patients in MET + GLI group completed study. A statistically significant reduction in RBS and FBS was seen in all the groups. MET + GLI treatment showed a statistically significant reduction in RBS at third month as compared to other groups.Study demonstrated that combination of Metformin+Glimepiridetreatment was more effective than Metformin+Glibenclamide and Metformin alone in reducing Fasting blood sugar and Random blood sugar. Thus Combination therapy of Metformin with Glimepiride seems to be a better treatment in patients having Type 2 diabetes.

KEYWORDS: Metformin plus Sulfonylureas, Combination therapy, Type 2 Diabetes.

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I. INTRODUCTION

Type 2 diabetes is a heterogeneous metabolic disorder which is characterized by common feature of chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism. It is a leading cause of morbidity and mortality world over. In India, it's incidence is estimated at 7% of adult population (approximately 65 million affected people), largely due to genetic susceptibility combined with changing life style of low-activity high-calorie diet in the growing Indian middle class. It is anticipated that by the year 2030 the number of diabetes globally will double from the present figure of 250 million. As a consequence of hyperglycemia of diabetes, every tissue and organ of the body undergoes biochemical and structural alterations which accounts for the major complications in diabetics. Appropriate glycemic control is a crucial factor in minimizing long-term micro and macro-vascular complications [1]. Usually, the approach is to initiate monotherapy first, followed by combination therapy which combats atleasttwo pathophysiological mechanisms causing T2DM. So there is a necessity to gradually intensify therapy in order to reach and maintain glycemic control [2].

II. MATERIALS AND METHODS

2.1. Study site:
The study was carried out at the outpatient department of RIMS - A Tertiary Care Teaching Hospital in Cuddapah, Andhra Pradesh, India.

2.2. Study duration:
Study was conducted for six months ranging from August 2017 to January 2018.

2.3. Study design:
Prospective,Observational, Open labelled, single centric study.

2.4. Study material:
Patient data collection proforma was designed to collect the details of the patients recruited in the study. (Annexure).

2.5. Inclusion criteria

1. Patients of either gender of age group between 18-75 years.
2. Patients who are willing to participate in the study and have written consent for study.
3. Patients with previous and family history of diabetes under mono or dual therapy with metformin alone or metformin + sulfonylureas respectively.

2.6. Exclusion criteria

1. Subjectswho are not willing to participate inthe study.
2. Subjects who are incapable of giving informed consent for the study.
3. Subjects less than 18years of age were excluded.
4. Pregnant or breast feeding women.
5. Subjects on other combinational therapies for treatment of diabetes.
6. Patients with any other serious concurrent illness.

After complete explanation of study procedures to the patients, a written consent from them was obtained. Total 70 patients were recruited randomly in the study as per inclusion and exclusion criteria and subjects were assigned into three groups as shown in Table 1, with the time span of three months.The patients received either 500 mg of Metformin alone twice daily (Group MET), 500 mg of metformin twice daily in combination with 1 or 2 mg of Glimepiride once daily (Group MET + GLI) and 500 mg of Metformin twice daily in combination with 5 mg of Glibenclamide once daily (Group MET + GLIB). Measurement of RBS and FBS at baseline was done. Glycemic Profile were measured at each follow-up (one month) of patient. Data was collected in patient data collection proforma (annexure) and was converted into Excel spread-sheet. Descriptive statistics were expressed as the mean value ± Standard Deviation (SD)and percentage. The categorized values were analyzed using paired and unpaired student t-test by Graph-pad prism.

III. RESULTS

3.1. Allocation of subjects into groups

A total 70 patients as per eligibility criteria were enrolled in the study. Among them, 6 from group-1 and 2 from group-2 were dropped out because of loss of follow up. Therefore, total 62 patients, 24 from group-1, 18 from group-2 and 20 from group-3 completed study as shown in table 1.

Table 1: Allocation of subjects into groups

S.no	Group	No.of patients recruited		No.of patients dropped	No.of patients completed	Total
		Male	Female			
1.	MET	13	11	6	24	n= 62
2.	MET + GLI	8	10	2	18	
3.	MET + GLIB	11	9	0	20	

3.2. Distribution of patients based on our study disease

Out of 62 (100%) patients 36 (51.61%) patients were diagnosed only with T2 DM, remaining 26 (41.93%) patients were diagnosed with other co morbidities along with T2 DM which was shown in below table-2.

Table 2: Patient distribution based on study Disease

S.no	Patients with T2DM		Patients with other comorbidities		Total
	Male	Female	Male	Female	
1.	11	13	21	17	**n = 62 (100%)**

Table 3: Distribution of diabetic patients based on their co-morbidities

S.no.	Patients with co-morbidities	Male	Female	Total
1.	T2DM with HTN	11	7	18 (47.36%)
2.	T2DM with MI	0	2	2 (5.26%)
3.	T2DM with COPD	2	0	2 (5.26%)
4.	T2DM with CHF	3	5	8 (21.05%)
5.	T2DM with Stroke	5	3	8 (21.05%)
	Total	21	17	**n = 38 (100%)**

3.3. Assessment of therapeutic efficacy among three groups

Patients in Group-MET showed reduction in FBS from140.1 ±7.92 at baseline to126.8 ±10.17 at last follow-up, RBS from 197.9 ±21.43 at baseline to 172.7 ±13.62 at last follow-up (table 4), While in Group MET+GLI showed Reduction in FBS from 147.4±15.34 at baseline to104.61±11.2 at last follow-up, RBS from 243.16±45.08 at baseline to 150.8±15.37at last follow-up (table 5) where as in Group MET+GLIB showed reduction in FBS from 135.2±9.007 at baseline to 115±12.9 at last follow-up, RBS from 208.14±26.85 at baseline to 169±15.52 at last follow-up (table 6).

Table 4: Change in RBS & FBS in Group-MET at various follow-ups

Parameters (mg/dl)	Group MET (mean ± SD)				
	Baseline	Follow-up 1	Follow-up 2	Follow-up 3	% reduction
FBS	140.1 ±7.92	135.1 ±8.84	131.6 ±9.93	126.8 ±10.17	9.4
RBS	197.9 ±21.43	189.7 ±18.13	183.9 ±18.38	172.7 ±13.62	12.9

Table 5: Change in RBS & FBS in Group-MET + GLI at various follow-ups

Parameters (mg/dl)	Group MET + GLI(mean ± SD)				
	Baseline	Follow-up 1	Follow-up 2	Follow-up 3	% reduction
FBS	147.4±15.34	134±11.2	120.33±11.57	104.61±11.2	29
RBS	243.16±45.08	219.72±34.68	188.05±28.51	150.8±15.37	37.9

Table 6: Change in RBS & FBS in Group-MET + GLIB at various follow-ups

Parameters (mg/dl)	Group MET+ GLIB (mean ± SD)				
	Baseline	Follow-up 1	Follow-up 2	Follow-up 3	% reduction
FBS	135.2±9.007	128.35±10.05	122.42±11.47	115±12.9	14.9
RBS	208.14±26.85	195.42±24.67	180.35±16.58	169±15.52	18.8

Mean reductions in FBS and RBS from baseline were statistically significantly with combination groups compared with MET alone treated group ($p<0.0001$).Hence Group MET+GLI showed better reduction in glycemic levels compared to other groups. The percentage decrease in FBS and RBS were 9.4% and 12.9% respectively in MET group as compared to 29%, 37.9% and 14.9%, 18.8% respectively in MET+GLI and MET+GLIB group as shown in figure 1.These data supports that combination of Metformin &Glimepiride capable to control glycemic levels to a greater extent as compared to combination of Metformin+Glibenclamide and Metformin alone.

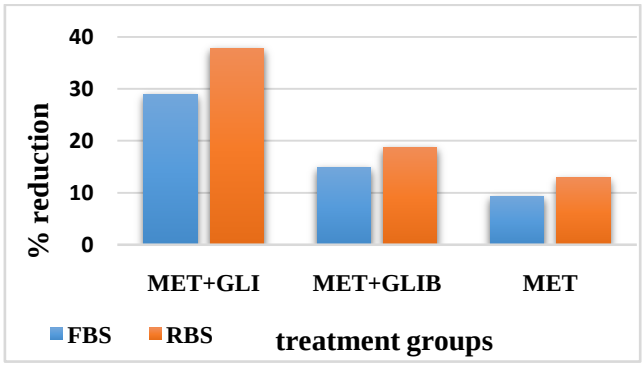

Figure 1: % Reduction in FBS and RBS levels at Baseline to last follow-up.

IV. DISCUSSION

This study indicates the efficacy of combination therapy of metformin with glimepiride in T2DM patients and result shows that % reduction in FBS and RBS were 9.4% and 12.9%, 29% and 37.9%, 14.9% and 18.8% in MET,MET+GLI,MET+GLIB groups respectively.Present guidelines from the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) endorse early initiation of metformin as a first-line drug for monotherapy and combination therapy for patients with T2DM [3,4]. The combination of metformin and sulfonylurea (SU) were one of the most frequently used and able toachieve a greater reduction in plasma glucose levels than either drug alone [5]. The combination ofglimepiride/metformin

results in a lower fasting blood sugar levels and less hypoglycemic events when compared to the combination of glibenclamide/metformin [6,7].

Second-generation sulfonylureas (SU) were most efficacious and cost-effective options for the therapeutic management of diabetes and bind to sulfonylurea receptors found on the surface of pancreatic β-cells leads to closure of K+-ATP channels, thus cell membrane is depolarized and insulin is released [8,9]. Glimepiride is different from the traditional SU drugs and sometimes classified as a third-generation as reported to have some extra-pancreatic effects, such as improving peripheral glucose uptake in muscle and decreasing endogenous glucose production in liver through these effects, glimepiride is reflected to have therapeutical benefit in the management of type 2 diabetes compared with other older generation sulfonylureas (e.g. glibenclamide).In present study MET+GLI group was associated with a greater reduction of glycemic levelsand evidenced that the combination therapy provided effective glycemic control than monotherapy in T2DM patients.

V. CONCLUSION

To maintain glycemic control and disease progression in T2DM, it is needed to shift from monotherapy to combination therapy. In our study, Metformin and glimepiridecombination was found potent in decreasing plasma glucose levels and target two different pathophysiological mechanisms causing T2DM compared to metformin plus glibenclamide and metformin alone and MET + GLI was found to be effective therapeutic option for patients with T2DM.

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