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OPEN LABELLED RANDOMIZED COMPARATIVE STUDY OF EMPAGLIFLOZIN AND METFORMIN COMBINATION V/S METFORMIN AND GLIMIPIRIDE COMBINATION IN KNOWN TYPE II DIABETES MELLITUS PATIENTS

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ABSTRACT

The current focus of research is an antidiabetic agent – SGLT-2 inhibitor(Empagliflozin) that can improve glycemic control without increasing hypoglycemia, can promote weight loss. The purpose of this study is to evaluate the efficacy of empagliflozin and metformin combination therapy compared with metformin and glimepiride combination therapy in patients with type II diabetes mellitus. A Randomized, Open Labeled, Parallel Group, Prospective Study was conducted from Dec 2016- May 2017 at a 350-beded Tertiary Care teaching hospital in South India.A total of 140 Patients with HBA1C ≥ 7% were divided into Group A and Group B. The primary end point was the change in FPG, PPG, HBA1C level from baseline at week 24. Key secondary end points were changes were from baseline in Body Weight, BMI, BP at week 24. At week 24 mean changes from baseline in FPG were: in Group A 168±64.9, in Group B 185±63.4; PLPG were: in Group A 141±84.08, in Group B 141±84.33; HBA1C were: in Group A -1±0.3,in Group B -1±0.3; SBP: in Group A -11±11.1, in Group B 9±11.5; BMI, Body Weight were reduced. Hypoglycemic attacks were reported in Group A. Urinary tract infections were reported in Group B.Empagliflozin 10 mg OD for 24 weeks as an add on therapy to metformin and glimepiride combination compared with metformin and glimepiride combination resulted in similar changes in HBA1C, FPG, PPG, Body Weight, BMI and BP and was well tolerated.

KEYWORDS: Diabetes Mellitus, Empagliflozin, Metformin, Glimepiride.

INTRODUCTION

Treatment of type 2 diabetes (T2DM) continues to present challenges, with significant proportion of patients failing to achieve and maintain glycemic targets. Despite the availability of many oral anti diabetic agents, therapeutic efficacy is offset by side effects such as weight gain and hypoglycemia. Therefore, the search for novel therapeutic agents with an improved benefit-risk profile continues. SGLT2-inhibitors are a new class of oral anti diabetics, which reduce hyperglycemia by increasing urinary glucose excretion independently of insulin secretion or action.

The kidney plays a major role in glucose homeostasis because of its role in gluconeogenesis and the glomerular filtration and reabsorption of glucose in the proximal convoluted tubules. Approximately 180 g of glucose is filtered daily in the glomeruli of a normal healthy adult. Typically, all of this glucose is reabsorbed with <1% being excreted in the urine. The transport of glucose from the tubule into the tubular epithelial cells is accomplished by sodium-glucose co-transporters (SGLTs). SGLT2 is a high-capacity, low-affinity transporter expressed chiefly in the kidney. It accounts for approximately 90% of glucose reabsorption in the kidney and has thus become the focus of a great deal of interest in the field of diabetes mellitus. SGLT2 inhibitors block the reabsorption of filtered glucose leading to glucosuria. This mechanism of action holds potential promise for patients with type 2 diabetes mellitus (T2DM) in terms of improvements in glycaemic control. In addition, the glucosuria associated with SGLT2 inhibition is associated with caloric loss, thus providing a potential benefit of weight loss.

Therefore, the current focus of research is an antidiabetic agent that can improve glycemic control without increasing hypoglycemia, can promote weight loss, improve β- cell function, while reducing complications and mortality associated with the disease SGLT2 inhibitors offer an entirely novel, insulin-independent approach for treatment of diabetes by blocking the reabsorption of glucose in the renal nephron resulting in markedly increased glycosuria and reduced blood glucose concentrations. Since this mechanism is not constrained by the extent of insulin resistance or beta-cell dysfunction, these drugs are ideal candidates to be used at any stage in the natural history of diabetes from newly diagnosed to long-standing disease, including extremes of insulin resistance and β-cell dysfunction. Their prospective use is further enhanced by the fact that these can be used as monotherapy for patients seeking

different treatment options and in complementary manner with other antidiabetic agents or insulin and is safe enough to be used in renal or hepatic compromise. What does all this new information about the SGLT2 drugs do to help us today? First, it holds the promise of new ways to individualize treatment of diabetes. This class of drugs has a novel mode of action that appears capable of adding a further glucose-lowering effect in combination with many other classes. This effect, typically in the range of 0.5 to 1.0% HbA1C, is clinically relevant although perhaps less than that of some other agents. By itself, it does not cause hypoglycemia. By causing loss of glucose in the urine, the SGLT2 agents favor weight loss, and by increasing clearance of sodium, they may assist in control of edema and hypertension.[6]

STUDY SITE

The study was conducted in the general medicine department of MNR medical college and hospital.

STUDY PERIOD

The study was carried out for a period of six months from December 2016 – May 2017.

STUDY DESIGN

A Randomized, Open Labeled, Parallel Group, Prospective study.

STUDY CRITERIA

Inclusion Criteria

i. Patients undertaking treatment with anti diabetics medication.
ii. Patient willing to participate in our study.

Exclusion Criteria

i. Patients with type 1 diabetes mellitus, patients with any other change in medication for diabetes(except insulin).
ii. Pregnant women are excluded.

STUDY APPROVAL

The study protocol was submitted to the medical superintendent of the hospital. The authorization from the medical superintendent was obtained and were permitted to carry on the study and utilize the hospital facilities required for the study.

STATISTICAL ANALYSIS

After collection of the data, results were obtained and the laboratory investigations and other parameters (Fasting Plasma Glucose, Post Prandial Glucose, HBA1C, BMI, Body Weight, Blood Pressure.)obtained were evaluated using MEAN and STANDARD DEVIATION method, to find out the difference between two treatment groups.

RESULTS

Table 4.1: Treatment Groups.

GROUP A (Metformin+Glimipiride)	GROUP B(Metformin+Glimipiride +Emapgliflozin)
70 Patients	70 Patients

In this 24 – week study, a total of 140 patients were divided equally into 70 Patients per group. Group A patients received Metformin (500mg BD & TID) with Glimepiride (1mg BD & TID) combination therapy & Group B patients received Metformin (500mg BD) with Glimepiride (1mg BD) along with emapgliflozin (10 mg OD) (add on) combination therapy.

Table 4.2: Demographic Details (Gender wise Distribution).

Gender	Total No. of Patients-140	Group A (70patients)	Group B (70patients)
Male Patients	71(50.7%)	32(45%)	39(55%)
Female Patients	69(49.2%)	38(54%)	31(44%)

Table 4.3: Demographic Details (Age Wise Distribution).

Treatment Groups	30-45yrs	46-55yrs	56 -65yrs	66-75yrs	76-85yrs
GroupA (70 patients)	2(2%)	1(1%)	5(7%)	19(27%)	43(61%)
Male(32)	1(1%)	0	0	9(12%)	24(34%)
Female(38)	1(1%)	1(1%)	5(7%)	10(14%)	19(27%)
Group B (70 patients)	0	0	4(5%)	14(20%)	52(74%)
Male(39)	0	0	4(5%)	7(10%)	27(38%)
Female(31)	0	0	0	7(10%)	25(35%)
Total(140)	2(1%)	1(0.7%)	9(6%)	33(23%)	95(67%)

Table 4.4: Body weight Mean and standard deviation value.

Body Weight	Mean of Group A	Mean of Group B	Standard Deviation of Group A	Standard Deviation of Group B
Baseline Value	79	78	7	5
6^{th} Month Value	65	50	6	3

Body Weight (Kgs) was noted and Mean and Standard Deviation was calculated for two Groups (A & B) and the weight was noted as the baseline values at the starting of the study and study end point values were noted as 6th month values. The mean and standard deviation changes of Group A were 10±1; mean and standard deviation changes of Group B were 28±2. Group B was more beneficial than Group A in reducing Body weight (kgs). Standard Deviation differences between two groups was 3 (Group A > Group B).

Table No. 4.5: BMI Mean and Standard Deviation.

BMI	Mean of group A	Mean of group B	Standard Deviation Group A	Standard Deviation Group B
Baseline Value	**27.0**	**28.2**	**4.3**	**3.9**
6th Month Value	**24.8**	**25.6**	**3.5**	**3.8**

BMI was calculated for two Groups (A & B) and the BMI Mean and Standard Deviation Values were noted as the baseline values at the starting of the study and study end point values were noted as 6th month values. The mean and standard deviation changes of Group A were 2.2±0.8; mean and standard deviation changes of Group B were 2.6±0.1. Mean changes: Group A Baseline values were < Group B Baseline values; at end point 0.8 difference was noted in between two groups. Standard deviation: Baseline values of Group A were > Group B Basline values. Difference noted: 0.4; end points showed 0.3 difference between two treatment groups (Group B > Group A).

Table No. 4.6: Fasting Glucose Mean and Standard Deviation Values.

Fasting Plasma Glucose	Mean of (Group A)	Mean of (Group B)	Standard Deviation Group A)	Standard Deviation Group B)
Baseline Value	295	292	68.24482	67.75274
3rd Month	161	160	23.85299	25.0441
6th Month	107	107	3.336231	3.467238

Fasting Plasma Glucose Mean and Standard Deviation was calculated for two Groups (A & B) and the Values were noted as the baseline values at the starting of the study, in between at 3rd month the values were noted as 3rd month values and study end point values were noted as 6th month values. The mean and standard deviation changes of Group A were 168±64.9; mean and standard deviation changes of Group B were 185±63.4. Mean changes: Group A Baseline values were > Group B. End points of both the groups were same. Standard

Deviation: Difference between two groups at end point noted as 0.1 at the end of the study (GroupB>GroupA).

Table No. 4.7: Post Prandial Glucose Mean and Standard Deviation Values.

Post Prandial Glucose	Mean of (Group A)	Mean of (Group B)	Standard Deviation Group A)	Standard Deviation Group B)
Baseline Value	299	299	92.65885	92.65885
3rd Month	238	239	40.3359	39.30983
6th Month	158	158	8.575822	8.337349

Post Prandial Glucose Mean and Standard Deviation was calculated for two Groups (A & B) and the Values were noted as the baseline values at the starting of the study, in between at 3rd month the values were noted as 3rd month values and study end point values were noted as 6th month values. The mean and standard deviation changes of Group A were 141±84.08; mean and standard deviation changes of Group B were 141±84.33. Mean changes: Group A Baseline values were =Group B. End points of both the groups were same. Standard Deviation: Difference between two groups at end point noted as 0.2 at the end of the study (Group A > Group B).

Table No. 4.8: HBA1C Mean and Standard Value.

HBA1C	Mean of (Group A)	Mean of (Group B)	Standard Deviation Group A)	Standard Deviation Group B)
BaselineValue	8	8	0.439614	0.439614
3rd Month	7	8	0.415111	0.432167
6th Month	7	7	0.130939	0.130939

HBA1C Mean and Standard Deviation was calculated for two Groups (A & B) and the Values were noted as the baseline values at the starting of the study, in between at 3rd month the values were noted as 3rd month values and study end point values were noted as 6th month values. The mean and standard deviation changes of Group A were -1±0.3; mean and standard deviation changes of Group B were -1±0.3. Mean changes: Group A Baseline values were = Group B. End points of both the groups were same. Standard Deviation: Difference between two groups at end point noted as 0 at the end of the study. (Group B =Group A).

Table No. 4.9: Blood Pressure Mean and Standard Deviation Values.

BLOOD PRESSURE	Mean of (Group A)	Mean of (Group B)	Standard Deviation Group A)	Standard Deviation Group B)
Baseline Value	137/85	135/85	14.6/5.9	15.2/5.9
3rd Month	135/85	135/85	4.1/3.7	4.2/3.8
6th Month	126/83	126/83	3.5/3.2	3.7/3.3

Blood Pressure (Systolic/Diastolic) was noted down for two Groups (A & B) and the Values were noted as the baseline values at the starting of the study, in between at 3rd month the values were noted as 3rd month values and study end point values were noted as 6th month values. The Systolic mean and standard deviation changes of Group A were -11±11.1; mean and standard deviation changes of Group B were 9±11.5.

Mean changes (SBP): Group A Baseline values were >Group B. End points of both the groups were same. Standard Deviation: Difference between two groups at end point noted as 0.2 at the end of the study (Group B > Group A).

No differences were in mean and standard deviation in DBP.

Table 4.11 GFR (estimated using Cockcroft -Gault Equation).

GFR NORMAL RANGE -120-150ml	MALE PATIENTS (71)	FEMALE PATIENTS(69)
Baseline Value (120-150)	69(98%)	66(95%)
6th Month Value (120-150)	67(94%)	64(92%)

Table 4.12 Cost Analysis of both treatment Groups.

TREATMENT GROUP A	TREATMENT GROUP B
Rs.68/10 tablets (metformin+glimepiride)	Rs.68/1tablets +Rs.480/10tablets Tablets(metfromin+glimepiride+empagliflozin)

Table 4.13: Other Antidiabetic Medications (As An Add On Therapy).

GROUP A (70)	GROUP B (70)
Linagliptin 5mg OD -1 patient (1.42%)	**Glipizide 5mg – 10 patients(14.28%)**
Glipizide 5 mg – 30 patients(42.85%)	

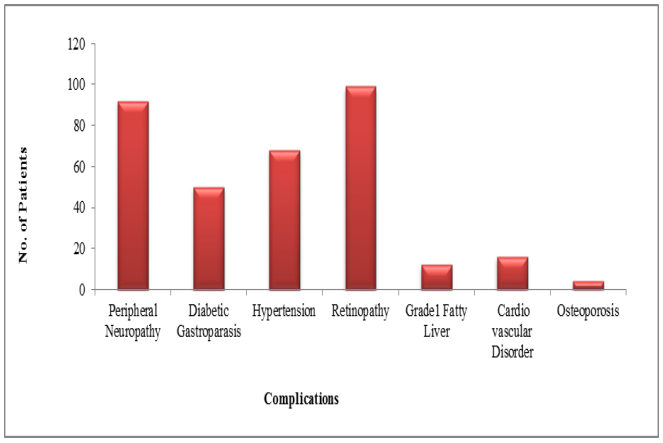

Figure No. 1. Type 2 Diabetes Mellitus Patients diagnosed with Complications.

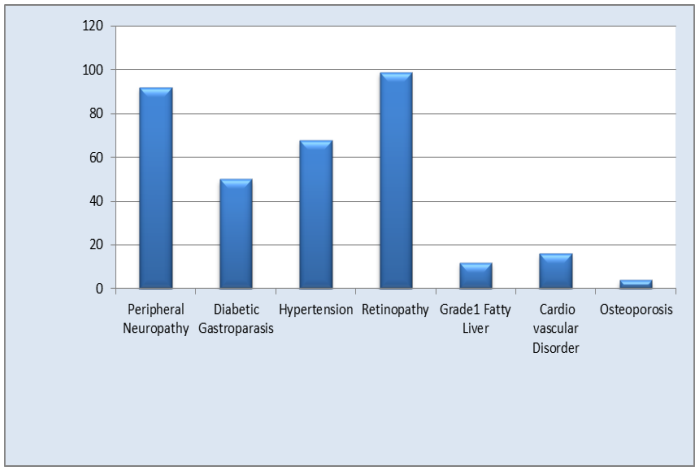

Figure No.2. Adverse Effects.

DISCUSSION

The current study was undertaken to assess the efficacy of emapgliflozinas an add on therapy to the metformin and glimepiride combination compared with metfromin and glimepiride combination therapy.

The findings in another study, which found that 12 weeks treatment with Empagliflozin monotherapy resulted in reductions in HBA1C, FPG and body weight were seen.[9]; in this study reductions in HBA1C- were equal in both the groups, reductions in FPG levels - Group A was effective in treating FPG levels, reductions in PPG levels - Group B was effective in treating PPG levels; these findings were noted in between two treatment groups; where as in other studies: reductions in HBA1C, FPG, PLPG and body weight were consistent with those reported from 12 week studies with other SGLT-2 inhibitors.[8]

The potential for reduction in body weight is a notable feature of SGLT2 inhibitor[10] and may make them useful agents to combine with other antidiabetic therapies to reduce glucose levels further and facilitate weight loss or mitigate any weight gain associated with improved glyceamic control.[11]

GFR was estimated using Cockcroft equation as a safety measure, in both the treatment groups.

There are a number of potential limitations to this study, including its short duration of 24 weeks and sample size of 140 participants. The study is further continued to assess the tolerability of empagliflozin.

In summary, the results of this study show that empagliflozin as an add on therapy to metformin and glimepiride combination compared to metformin and glimepiride combination: reductions in glycemic levels were almost similar or not much effective, empagliflozin group had an additional benefit of reductions in weight loss and empagliflozin was well tolerated except for urinary tract infections.

CONCLUSION

Diabetes Mellitus is a chronic illness that requires a combination of pharmacological and non-pharmacological measures for better glycemic control. Patient adherence to the therapy and lifestyle modification plays an important role in diabetes management. Most of the patients were diagnosed with complications of diabetes mellitus, which indicates poor management of the diabetes mellitus. All the 140 patients had poor management of plasma glucose levels, after the administration of the combination therapy of metformin and glimipiride in Group A and empagliflozin as an add on therapy to metformin and glimipiride in Group B, both the groups had similar or no much difference in Fasting plasma glucose, Post prandial glucose and HBA1C levels. In few efficacy parameters Group A was more effective than Group B. As the study was not long term study the effect of empagliflozin assessed was not significant. Mainly hypoglycemia were reported most commonly in Group A patients when compared to group B patients.

However, this study concludes that Group A (Metformin+Glimepiride) was effective in reducing the poorly controlled glycemic levels and reduces cost burden to the patient than Group B (Metformin+Glimepiride+Empagliflozin) which was effective as Group A in

reducing the glycemic levels, but increases burden to patients cost of treatment. This study will be continued to assess the effect of empagliflozin on diabetes mellitus because of its unique advantages and mechanism of action.

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