Research Article

Efficacy and Safety of Dapagliflozin: Report from A Tertiary Care Hospital of Karnataka

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ABSTRACT

Managing type 2 diabetes has its own challenges. The age old treatment has seen scientific innovations time and again. One such addition is dapagliflozin, an investigational sodium glucose cotransporter 2 inhibitor, as an add-on therapy for better glycemic control in patients inadequately controlled with metformin. The present study is an attempt to evaluate dapagliflozin and comment on renal safety of the drug. The study was conducted at Adichunchanagiri Institute of Medical Sciences, Karnataka, on 200 diagnosed cases of T2DM who were already on metformin. All were given dapagliflozin. They were divided in 2 equal groups randomly. One of the groups was given an additional hypoglycemic agent apart from these two drugs. They were evaluated at 6th and 12th month follow-up. The result showed that there was a significant reduction in HbA1c levels after 12 months of treatment with dapagliflozin as an add-on therapy. Regarding renal safety, serum creatinine was used as a surrogate marker. During the follow-up visits, there was no significant change in creatinine levels for patients of both the groups. Moreover, microalbumin levels significantly reduced in patients who received dapagliflozin and metformin. The drug also had a significant impact on weight reduction. Conclusion: Dapagliflozin, a SGLT2 inhibitors promises to have better glycemic control when used as an adjuvant with metformin with least renal hazard and good weight reduction.

Keywords: SGLT2 inhibitor; dapagliflozin; efficacy; renal safety; type 2 diabetes mellitus.

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INTRODUCTION

Diabetes Mellitus has emerged as a global pandemic with ever-growing proportions. The estimated global prevalence according to last report of International Diabetes Federation is 463 million people and this is expected to reach over 700 million by the year 2045.[1] The majority cases of Diabetes Mellitus is Type 2 diabetes (T2DM). The pathophysiology delineated behind this condition of T2DM is typically characterized by impaired insulin action due to growing resistance and gradual decline in β-cell function leading to hyperglycemia.[2] A state of chronic hyperglycemia in the body causes multiple damage to the micro as well as macrovasculature, ultimately increasing chances of mortality.[3] A basket of hypoglycemic drugs are available to address these problems, choice depending on various factors of patients like age, comorbidities etc. But none of the available therapeutic options come without limitations. Hence, timely management of the disease to prevent development of any complication poses unique challenges.

To this basket of choices of oral hypoglycemic agents, we have a recent addition as Sodium–glucose cotransporter 2 (SGLT2) inhibitors. This novel class of drugs come with an insulin-independent mode of action. These transport channels are primarily involved in resorption of glucose in the proximal convoluted tubule. Hence, inhibiting these channels leads to resultant glucosuria and eventually lowering of blood glucose levels. SGLT2 inhibitors approved for use or under consideration include dapagliflozin, canagliflozin, empagliflozin and ipragliflozin. Among these, dapagliflozin has received marketing authorization in many parts of the world.[4]

Dapagliflozin is recommended as monotherapy for maintenance of sugar levels in patients of T2DM besides lifestyle modification. It is indicated for patients who can not tolerate metformin or in cases where metformin is contraindicated. It can also be prescribed along with other glucose-lowering agents including insulin to attain adequate glycaemic control.[5] Different bodies have suggested dosage and monitoring profile of the drug.[5-7] Various studies across the globe has evaluated this drug at doses starting from 1 to 50 mg along with lifestyle modification; and compared the response with groups on metformin monotherapy. The results have been convincing enough to recommend dapagliflozin as a monotherapy with remarkable reduction in glycosylated hemoglobin levels.[8-13]

The aim of this study was to evaluate the efficacy and safety of dapagliflozin among diagnosed cases of T2DM attending a tertiary care hospital of Karnataka.

MATERIALS AND METHODS

The current observational study was planned and conducted by Department of General Medicine, Adichunchanagiri Institute of Medical Sciences, Mandya, Karnataka. The objective of conducting the study was to determine the effectiveness and renal safety of dapagliflozin. For the purpose of the study, inclusion criteria were: diagnosed cases of T2DM and those patients who were on metformin with or without another insulin lowering agent. Based on these criteria, list of patients was created and two groups were divided randomly such that each group had 100 patients each. All the patients were given 10 mg of dapagliflozin once daily along with metformin 1.5–2.5 g/day. Group B patients were on another agent apart from these two drugs, as before. Approval was obtained from the Institutional Ethics Committee before initiation of the data collection phase. Patients were included in the study after obtaining informed consent forms from each of them. Another inclusion criteria considered for the study: patients who agreed to continue the therapy with no interruption in the course, normal renal function before the initiation of treatment and adapt necessary lifestyle modifications were included. They were followed up for 12 months and only patients who adhered to the required criteria were included in the final analysis. Patients were motivated and counseled to continue with the therapy and lifestyle modifications during each visits.

Baseline characteristics included age, sex, weight and height for BMI, systolic blood pressure, diastolic blood pressure, and disease duration. Effectiveness was assessed using the change from baseline in HbA_{1c} at 6 and 12 months as well as changes in body mass index (BMI) and lipid parameters (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides) at 12 months. HbA_{1c} was self-monitored, with outpatient visits performed every three months or when needed. Renal function was assessed by the change in blood creatinine levels at 6 and 12 months, as well as urine microalbumin levels at 12 months.

Statistical analyses were performed using SPSS Statistics version 20 (IBM, Chicago). All variables were analyzed separately in patients of group A and group B. Results of descriptive statistics has been expressed in terms of mean and standard deviation (SD). Frequency distribution tables or figures has been given, as appropriate. A p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 200 patients were included in the study with 100 in each group. Complete data after follow up could be obtained from 87 patients of group A and 93 patients of group B. Hence, final analysis was done on these patients only. The mean age of the patients was 51.7 and 53.8 years in Group A and B, respectively. There was a male preponderance noted in both the groups. Overall, majority of the patients had BMI on higher side. The overall mean duration of disease was 6.4 years, ranging from 3 to 12 years. Prior history of myocardial infarction was noted among 12.7% of the study participants (23/180), majority of them were male (15/23). Baseline data and demographic details of patients from both the groups has been given in table 1. Co-morbidities like hypertension and dyslipidemia were managed by keeping patients concomitantly on drugs like angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers for hypertension, and statins for management of dyslipidemia. Comparability of groups was checked by t test being performed for each one of the variable separately. Except for a few characteristics, there was no significant difference between both the groups [Table 1].

Table 1: Baseline demographic details and laboratory parameters of patients of both the groups

Characteristics	Group A (n = 87)	Group B (n = 93)	P value
Age (years)	51.7 ± 6.8	53.8 ± 5.4	> 0.05
Male, (%)	71.3%	76.3%	> 0.05
BMI (kg/m^2)	29.9 ± 5.4	31.3 ± 6.2	> 0.05
Duration of disease (years)	6.8 ± 2.4	8.2 ± 3.5	> 0.05
Systolic BP (mm of Hg)	141.2 ± 19.3	139.7 ± 17.5	> 0.05
Diastolic BP (mm of Hg)	86.4 ± 5.7	83.8 ± 6.2	> 0.05
Creatinine (µmol/L)	75.3 ± 11.2	76.5 ± 16.7	> 0.05
Microalbumin (µg/mg)	112.6 ± 73.4	82.4 ± 53.5	**< 0.05**
eGFR (mL/min)	92.4 ± 22.5	94.6 ± 20.1	> 0.05
Total cholesterol (mg/dl)	180.2 ± 19.3	183.4 ± 23.4	> 0.05
LDL (mg/dl)	116.3 ± 23.4	112.3 ± 21.2	> 0.05
HDL (mg/dl)	53.4 ± 11.3	52.3 ± 6.7	> 0.05
Triglycerides (mg/dl)	139.4 ± 54.3	135.6 ± 58.8	**< 0.05**
Established CVD (N)	21	24	> 0.05
Prior Myocardial infarction (N)	7	13	**< 0.05**

HbA1c levels at the initiation of the study was compared using t-test and there was no significant difference between both the groups. For patients during the course of the study, when added to metformin, dapagliflozin significantly reduced HbA_{1c} levels from baseline in patients of both the groups. After 6 months of treatment, HbA_{1c} levels decreased by 0.5% and 0.3% in group A and B, respectively. This reduction was statistically significant ($p < 0.05$). Similarly at 12 months of follow-up after treatment, HbA_{1c} levels decreased by 0.7% and 0.6% respectively in each group. In patients of group B, the difference in HbA_{1c} from baseline level was significantly higher when assessed at 6 months, however, no significant difference was observed from the baseline levels and the 12th months levels of HbA1c between patients from both the groups [Figure 1].

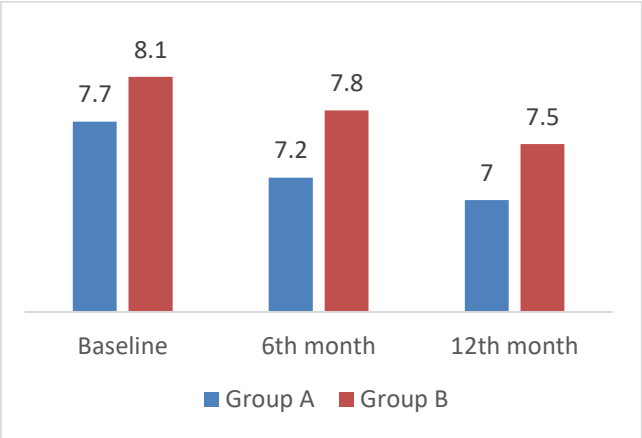

Figure 1: Bar diagram showing changes in HbA1C levels for both the groups during the study duration

Over the 12-month treatment period, dapagliflozin significantly reduced BMI in all the patients from their baseline levels. All the lipid parameters reduced towards their normal values over the study period for both the groups, however, these changes observed in lipid parameters were not significant. Moreover, a significant reduction in microalbumin was observed in group A patients after 12 months [Table 2].

Renal function was assessed by the difference observed in the creatinine levels. No adverse effects on renal function was noted during the course of the study as there was no significant difference in creatinine levels from the baseline and at 6 and 12 months in all patients [Figure 2]. The eGFR values constantly remained above 60 mL/min for all the patients from both the group throughout the course of the study.

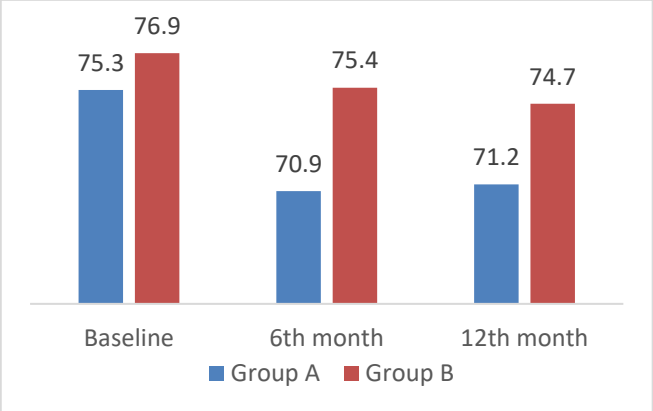

Figure 2: Bar diagram showing changes in serum creatinine (marker of renal function) separately for the patients from both the groups

Table 2: Table showing data of characteristic variable at 12th month duration with the change in the variable from the baseline data

Characteristics	Group A	Group B	P value*
BMI (kg/m²)	28.7 ± 5.2	29.3 ± 4.8	> 0.05
Change	-1.2	-2	
P value (change from the baseline value)	< 0.05	< 0.05	
Total cholesterol (mg/dl)	176.6 ± 28.9	178.2 ± 41.8	> 0.05
Change	-3.6	-5.2	
P value (change from the baseline value)	> 0.05	> 0.05	
LDL (mg/dl)	114.6 ± 21.1	109.4 ± 17.8	> 0.05
Change	-1.7	-2.9	
P value (change from the baseline value)	< 0.05	> 0.05	
HDL (mg/dl)	55.6 ± 7.2	54.5 ± 9.7	> 0.05
Change	+ 1.3	+ 2.2	
P value (change from the baseline value)	> 0.05	> 0.05	
Triglycerides (mg/dl)	118.2 ± 54.7	128.4 ± 46.7	< 0.05
Change	-21.2	-7.2	
P value (change from the baseline value)	< 0.05	> 0.05	
Microalbumin (µg/mg)	90.3 ± 82.6	78.7 ± 43.7	< 0.05
Change	-22.3	-3.7	
P value (change from the baseline value)	< 0.05	> 0.05	

* P value for the difference in parameters at 12th month follow-up

DISCUSSION

Dapagliflozin has showed efficacy in maintaining good glycemic control and side by side has known to be safe by many of the previous researcher. The current study was a humble attempt to add up to this pool of evidence on efficacy and renal safety of this SGLT2 inhibitor, dapagliflozin. It has been known to safe for both the genders, though there was a male preponderance noted in the current study, overall efficacy of the drug is promising.

The result showed that there was a significant reduction in HbA_{1c} levels after 12 months of treatment with dapagliflozin as an add-on therapy. In patients from both the groups, significant reductions were apparent from 6 months. Surprisingly, there was better control noted in patients who were on dapagliflozin along with metformin rather than those patients who were on additional hypoglycemic agent apart from these two drugs. Regarding renal safety, serum creatinine was used as a surrogate marker. Another biomarker used was urine microalbumin levels. During the follow-up visits, both were repeated and there was no significant change in creatinine levels for patients of both the groups. Moreover, microalbumin levels significantly reduced in patients who received dapagliflozin and metformin. The eGFR values constantly remained above 60 mL/min for all the patients from both the group throughout the course of the study. Apart from these, the drug also had a significant impact on weight reduction. All the lipid parameters also reduced after treatment, though the change was not significant apart from triglycerides in group A patients.

A double blinded placebo administered 102 week long trial also showed significant reduction in HbA1c levels with SGLT2 inhibitors.[14] They further continued their study and concluded that these drugs have additional glycemic control when administered in patients who were already on metformin.[15] Not only immediate effects but some of the researchers have reported a sustained glycemic control with dapagliflozin as compared to sulphonylurea.[16-18] Even among geriatric patients with known cardiovascular diseases, dapaglifozin has been known to maintain a healthy sugar levels alonga cardio-protective action by maintaining blood pressure.[19-21] Taking mortality into account was out of bound for the current study, this novel drug has been documented with lower mortality among patients with T2DM.[20-22]

The size of the study population was not large due to resource constraints but the researcher wishes to take forward this study on larger samples in future with a matched control group. One of the strengths of the study was a comparative good observational period and the fact that it was conducted in a real-life setting, hence, improving the generalization of the findings.

CONCLUSION

Dapagliflozin is an oral hypoglycemic agent that works on the principal by inhibiting SGLT2. It has been known to be effective as a monotherapy or in combination with agents including insulin. It has documented reduction in HbA1C levels among patients with longstanding T2DM. Side by side, it has been found to be association with remarkable reduction of weight when combined with lifestyle modifications. It is generally well tolerated and renal function remain unaltered. Though, it promises to have good glycemic control yet reports on long term outcomes are undercover.

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