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Original Article

Add-On Therapy of Dapagliflozin to Metformin in Patients with Diabetes Mellitus Type-2; Efficacy and Renal Safety

Benish Adil, Arshad Rabbani, Imran Arshad, Sualeha Ahmed, Muhammad Ali Khalid

Department of Medicine, Benazir Bhutto Hospital, Rawalpindi Pakistan

ABSTRACT

Objective: To study efficacy of Dapagliflozin in treatment of diabetes mellitus type-2.
Study Design: Quasi-experimental study.
Place and Duration of Study: Medical unit, Benazir Bhutto Shaheed Hospital, Rawalpindi Pakistan from Jan to Dec 2019.
Patients & methods: Patients taking Dapagliflozin in combination with Metformin (MET+DAPA) (n=45) were compared to those taking other glucose lowering agent in combination with Metformin (MET+ other drug) (n=45) for the control of diabetes mellitus type-II. Efficacy of treatment was assessed by the level of glycosylated hemoglobin HbA1c, and renal safety assessed by serum creatinine level done at 6 and 12 months of treatment.
Results: Total 90 cases were studied including 60% male and 40% female cases with mean age 50.8±7.4 years. Patients taking Dapagliflozin + Metformin (n=45), and others taking Metformin+ other glucose lowering drug (n=45) were having mean values of BMI 32.8±5.9 kg/m2 & 33.4±7.2 kg/m2, HbA1c 8.4±1.2% & 9.1±1.6 % and blood urea nitrogen 6.7±1.4 & 6.5±1.8 mmol/L respectively. After 12 months treatment mean HbA1c level was reduced from 8.7 ± 1.4% to 6.6 ± 0.3%, BMI reduced significantly and no detrimental effects reported on renal function.
Conclusion: Patients with type-II diabetes mellitus taking Dapagliflozin in combination with Metformin showed good glycemic control and renal safety.

Keywords: Dapagliflozin, Diabetes mellitus type-2, Glycosylated Hemoglobin, Metformin.

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INTRODUCTION

Diabetes mellitus type-2 is a multifactorial chronic metabolic disease and a great threat to public health. Its morbidity is increasing with time and according to an estimate its prevalence will be about 552 million by 2030. It is difficult to achieve good glycemic control among patients with typ-2 diabetes. Mostly patients taking anti-glycemic monotherapy are unable to achieve blood glycemic control. In such cases combination therapy of anti-diabetics has been suggested, which not only acquire glycemic control but also have good impact on cardiovascular and renal profile and reduces hypoglycemic events as well.[1] Prevalence of diabetes mellitus type-2 in Pakistan is 11.77%, prevalence is 11.2% in males and 9.19% in females. It is more common in urban areas than rural areas.[2] This disease is also common in western countries. Prevalence of diabetes mellitus in Italy has been increased from 3.4% to 5.5% in last 20 years and out of them 91% have type-2 diabetes.[3] Main goal of treatment of diabetes is to reduce blood glucose level.[4] In diabetes systemic metabolic dysregulation occurs and it is associated with increased BMI and obesity. Dapag-liflozin is a selective inhibitor of SGLT2 (sodium-glucose co-transporter-2) that decreases blood glucose level by decreasing renal absorption of glucose and increasing its excretion.[5] In phase-III trials dapag-liflozin was well tolerated in diabetes mellitus type-2 in early and late stages and no issue in its safety reported.[6,7] Studies have confirmed that Dapagliflozin has reduced serum HbA1c level and body weight as well when used alone as add-on therapy with other glucose lowering drugs.[8] Dapagliflozin in combination with Metformin does not affects renal function and has no renal toxicity among patients having normal or mildly impaired renal function. It causes glycosuria and lowers blood glucose level irrespective insulin sensitivity or secretion by β-cells. It also lowers blood pressure and body weight. It has been reported safe among diabetic patients with chronic kidney disease stage 3A, due to its beneficial renal effects.[9] Dapagliflozin with Metformin after 24 weeks treatment has been reported to have good metabolic effects such as increasing HDL level, decreasing triglyceride concentration and also lowers body weight among women with recent gestational diabetes mellitus.[10] This study was conducted to evaluate efficacy of Dapagliflozin in lowering serum glucose level and its renal safety in patients with type-2 diabetes in Pakistan.

Correspondence: Dr Benish Adil, Department of Medicine, Benazir Bhutto Hospital, Rawalpindi Pakistan
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METHODOLOGY

The quasi-experimental study to investigate the efficacy and renal safety of Dapagliflozin in patients with type-2 diabetes with disease duration <10 years, who were taking Metformin 1-2.5g daily. Patients reporting to the medical unit of Benazir Bhutto Shaheed Hospital Rawalpindi (study hospital) who took Dapagliflozin and Metformin for 12 months from January to December 2019 were analyzed. Two groups were created each containing 45 patients, one group taking DAPA+MET (group-A) and other taking MET+other drug (Group-B). Those taking insulin were not included in the study. Data of both groups was compared with each other. Study sample was selected using convenient sampling technique. Those patients were selected who used to come in outpatient clinic on follow-up properly in whole period of observation, showed compliance with treatment, not having any morbidity other than diabetes mellitus, took modified diet according to our advice and underwent all advised investigations in our outpatient clinic laboratory. The patients who were not able to test their blood glucose at home as advised, were not included in the study. Antidiabetic drugs other than insulin were added to Metformin in the group not taking Dapagliflozin. Ethical committee of study hospital was informed about study protocol and permission was taken to conduct the study (ERC/IERB Ltr no. 22155). Variables related to patients were analyzed such as age, gender, duration of disease, systolic and diastolic blood pressure. Efficacy of treatment was assessed by testing serum HbA1c for glycemic control and renal safety was assessed by serum creatinine level and eGFR at 6 and 12 months of treatment. Data was analyzed using SPSS software version 20. Data of both groups was analyzed, one who took Dapagliflozin+ Metformin and second group who took Metformin+ other glucose lowering drug. Results of both groups were compared with each other. Means and standard deviation were calculated for quantitative variables. Frequencies and percentages were calculated for qualitative variables. T-test was applied using 5% level of significance.

RESULTS

Data of 90 cases having diabetes mellitus type-2 was included in this study, including 54(60%) males and 36(40%) females. Age of patients was 20-70 years with mean age of 48.16±11.9 and 49.8±11.3 years in Group-A and B respectively. Before starting the treatment, mean baseline HbA1c of all cases was 8.34±0.65% in Group-A and 8.28±0.62% in Group-B and mean eGFR was 109.44±11.2 and 115.07±12.9 ml/min in both groups respectively. Patients were using anti-hypertensive, ACE (angiotensin converting enzyme) inhibitors, ARBs (angiotensin receptor blockers) and calcium channel blockers, and statins for hyperlipidemia. Mean body mass index was 32.8±5.9 among patients in group-A and 33.4±7.2 kg/m^2 among patients in group-B. At the start of treatment systolic and diastolic blood pressure and eGFR were measured in all study cases. Mean duration of disease in our study was 6.25±2.2 and 6.4±1.79 years in Group-A & Group-B respectively (Table-I).

Table-I: Baseline characteristics in both Groups at the Start of Treatment (n=90)

Baseline Characteristics	(Group-A) (n=45)	Group-B (n=45)	*p*-value
Age in years (Mean±SD)	49.89±11.39	48.16±11.903	0.482
Gender			
Male Female	26(57.8%) 19(42.2%)	28(62.2%) 17(37.8%)	0.520
Disease duration (years)	6.45±1.79	6.25±2.23	0.631
Systolic blood pressure	137.56±10.58	138.00±8.68	0.828
Diastolic blood pressure	88.89±4.63	88.33±4.39	0.561
Glycosylated Hemoglobin	8.34±0.65	8.28±0.62	0.693
Creatinine (umol/L)	80.73±8.23	81.82±5.64	0.466
Estimated glome-rular filtration rate (eGFR) (ml/min)	109.44±11.27	115.07±12.90	0.030

After first 6 months of treatment HbA1c, eGFR and creatinine were tested in patients of both groups. Outcomes of treatment of both groups were almost similar. Group-A showed significant lower HbA1c level than baseline (Table-II).

Table-II: Study Characteristics after 6 months of treatment (n=90)

Baseline Characteristics	Group-A (n=45)	Group-B (n=45)	*p*-value
Glycosylated Hemoglobin (HbA1c) (%) (Mean±SD)	7.15±0.34	7.39±0.45	0.006
Creatinine (umol/L)	81.53±8.33	82.36±5.92	0.591
Estimated glomerular filtration rate (eGFR) (ml/min) (Mean±SD)	110.53±10.33	116.04±11.41	0.018

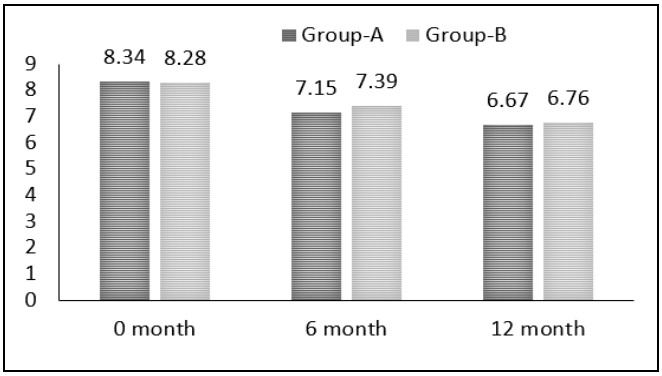
Patients in group-A were having serum creatinine 80.7, 81.5 and 81.8 umol/L at the start of treatment, after six months and then after 12 months of treatment respectively. Similarly patients in group-B were having these values as 81.8, 82.3 and 83.1 umol/L at the start, after six months and after 12 months of treatment (Table-III).

Table-III: Study Characteristics after 12 months of Treatment(n=90)

Baseline Characteristics	Group-A (n=45)	Group-B (n=45)	*p*-value
Glycosylated Hemoglobin (HbA1c)(%) (Mean±SD)	6.67± 0.31	6.76±0.24	0.128
Creatinine (umol/L)	81.80±7.92	83.11±6.05	0.380
Estimated glomerular filtration rate(eGFR) (ml/min)	110.96±9.66	115.36±10.58	0.042

Serum HbA1c level decreased in both groups and results were comparable. It was seen that decrease in HbA1c level was significant after 6 months of treatment. At the end of treatment decrease in HbA1c was almost similar in both groups (Figure). In Group-A and Group-B HbA1c level <7% was achieved in 87% and 74% cases respectively at the end of treatment.

Figure: Change in HbA1c Level during Study Period in both Groups (n=90)



DISCUSSION

Various oral glucose lowering agents are available, out of them Metformin is first line drug as recommended by American Diabetes Association and the European Association for the Study of Diabetes.[11] Dapagliflozin was the first SGLT2 inhibitor introduced into market. They not only lower HbA1c but also decrease body weight, lowers blood pressure & serum triglycerides level.[12] A study conducted by Majewski *et al*. reported significant decreased in mean systolic and diastolic blood pressure and increase in eGFR after using 25 mg empagliflozin (SGLT2 inhibitor) for 12 weeks.[13] Many studies have shown that Dapagliflozin as monotherapy or in addition to insulin or Metformin reduces glycosylated hemoglobin level significantly in patients with type-2 diabetes mellitus and improves glycemic control.[14-16] A study reported that Dapagliflozin reduced HbA1c from 4.3±1.7-4.1±1.1% & Metformin as alone therapy increased HbA1c from 4.4±2.0-5.7±2.4% after 16 weeks of treatment. Similarly serum HDL level was improved from 50.9±9.0-55.1±9.4 mg/dl, LDL level increased from 109.6±33.2-124±33.6 mg/dl and triglycerides increased from 142.8±53.1-145.2±69.0mg/dl.[17] In our study HbA1c was reduced from mean value 8.34±0.65% to 6.67±0.31%.[17] Fioretto *et al*. explained that Dapagliflozin improves renal function by decreasing reabsorption of sodium and glucose from proximal renal tubules hence decreasing intra glomerular pressure via tubuloglomerular feedback mechanism. This decreased transport of glucose from proximal renal tubules decreases oxidative stress, inflammation and tubuleinterstitial fibrosis as hyper filtration in diabetes type-2 leads to worsening of renal disease. Fioretto reported decreased in urine albumin/creatinine ratio by -57.2% to -43.8% in study group after use of Dapagliflozin 10mg and 5mg for 104 weeks.[18] Dapagliflozin has been found safe among elderly type-2 diabetic patients showing reduced rate of cardiovascular deaths with hazard ratio (HR) of 0.88%, 0.77% and 0.94% in age groups of <65, ≥65 to <75 and ≥75 years respectively. Safety parameters like fractures, cancer, volume depletion, urinary tract infections and amputations were equal for Dapagliflozin to placebo treatment while hypoglycemic events and acute renal injury was reduced.[19] A study was conducted in Italy on 66 type-2 diabetic patients who used Dapagliflozin and Metformin for 12 months which showed good glycemic control in 56% cases while in other cases (44%) an additional glucose lowering agent was added to reduce HbA1c.[20] While in our study good glycemic control achieved with Dapagliflozin and Metformin in 87% cases and with MET+Other agent in 74% cases. Further studies are required to determine long term side effects of Dapagliflozin.

CONCLUSION

Dapagliflozin is effective in lowering serum HbA1c level after 12 months of treatment without disturbing renal functions. After six months of treatment HbA1c blood level was significant reduced. Outcomes of treatment with Dapagliflozin with Metformin were almost same to those took Metformin with other glucose lowering drug.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

BA: & AR: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

IA & SA: Study design, critical review, drafting the manuscript, approval of the final version to be published.

MAK: Concept, data acquisition, data interpretation, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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