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Original Research Article

A Retrospective Observational Assessment of Dapagliflozin as an Add-On Therapy in Type-2 Diabetes Mellitus Patients

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Abstract

Aim: The aim of the present study was to assess the effectiveness of dapaglifozin in the management of T2-DM in combination with other hypoglycemic agents (OHAs) or insulin, in terms of improving HbA1c and fasting blood glucose, among diabetic patients.

Material & Methods: This study was a retrospective observational study conducted at department of Pharmacology, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India for one year. All adult diabetic patients who were prescribed Dapagliflozin during the period of one year, total 200 patients were included in the study. FBG, HbA1c collected through hospital records from General Medicine and Endocrinology. Patients who stopped drug before 3 months period were excluded.

Results: The mean age of patients was 54.46±6.14 years, in total 45 patients 70% (140) were male and 30% (60) were female. The mean fasting blood glucose and HbA1c levels at baseline were 9.31±0.77% and 182±32.88 respectively. In this study, all patients received dapagliflozin as an add-on therapy in combination with ongoing diabetic treatment. In the follow-up period, Paired T test was used to evaluate the difference in HbA1c and FBG following treatment with dapagliflozin. P values for the changes in FBG and HbA1c from baseline were significant (p=0.001 & p=0.001, respectively).

Conclusion: Dapagliflozin as an add-on therapy significantly reduced the HbA1c level and fasting blood glucose of Type-2DM patients, in a 3-month treatment period. Due to the frequency of genitourinary tract infections, caution is indicated while treating the patients.

Keywords: Dapagliflozin, SGLT-2 Inhibitor, Type-2DM, FBG, HbA1c

Introduction

Diabetes mellitus (DM) is one of the prevalent morbid conditions all over world and India. Day by day, increase in its prevalence is attributed to lifestyle derangements.[1] Diabetes is a chronic disease characterized by hyperglycemia that resulting from resistance to insulin, decreased or absent secretion of insulin, or both.2 The progressive nature of type [2] diabetes mellitus (T2DM) usually requires combination therapy with multiple antihyperglycemic agents (AHAs) for

achieving and maintaining glycemic control.3 The classic symptoms are excess thirst, frequent urination, and constant hunger. Treatment of hyperglycemia in patients with type 2 diabetes remains a challenge, particularly in those who require insulin as the disease progresses. [3,4]

Dapaglifozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor, a new class of oral antihyperglycemic drugs with an innovative mechanism of action, and is the second SGLT2 inhibitor to be approved by the Food and Drug Administration of the United States of America (FDA). Managing type 2-diabetes mellitus (T2-DM) with effective and tolerable oral agents will eventually decrease the devastating complications associated with uncontrolled T2-DM and ultimately improve quality of life. In 1990, a novel class of drugs to treat T2-DM with glucose urea was developed but was limited by poor bioavailability due to poor absorption as well as rapid degradation. [5-7] Dapagliflozin reduces plasma glucose by selectively and reversibly blocking the SGLT2 receptor and that acts by inhibiting tubular reabsorption of up to half of the glucose filtered by SGLT2 located at segments 1 and 2 in the proximal renal tubule, resulting in a dose-dependent increase in urinary glucose excretion and ultimately, an improvement in glycemic parameter encourages the filtration of glucose into the urine through the kidneys and remove it from the body. [8-10] Its C-aryl glucoside-derived chemical structure provides dapaglifozin with a prolonged pharmacokinetic half-life as well as a nearly 3000-fold selectivity for SGLT2 versus SGLT1, making it possible to administer dapaglifozin in an unmodified oral form without affecting SGLT-1-mediated glucose transport in other tissues. [11,12] In randomized clinical trials (RCTs), dapagliflozin demonstrated a significant improvement in glycemic control in relative to placebo when used as monotherapy, or as an adjunct to metformin, sulfonylurea (SU), sitagliptin, or insulin. [13] It was also demonstrated that dapagliflozin reduces body weight and blood pressure. Dapagliflozin well absorbed orally but absorption decreases if given along with fatty food. Dapagliflozin is approximately 91% protein bound. The metabolism of dapagliflozin is primarily mediated by UGT1A9. Dapagliflozin is not appreciably cleared by renal excretion, but its metabolites are primarily eliminated via the renal pathway. [14,15] Currently, this study aims to assess the effectiveness of dapaglifozin in the management of T2-DM in combination with other hypoglycemic agents (OHAs) or insulin, in terms of improving HbA1c and fasting blood glucose, among diabetic patients.

Material & Methods

This study was a retrospective observational study conducted at department of Pharmacology, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India. All adult diabetic patients who were prescribed Dapagliflozin during the period of one year, total 200 patients were included in the study. FBG, HbA1c collected through hospital records from General Medicine and Endocrinology. Patients who stopped drug before 3 months period were excluded. The study was conducted for the duration of 1 year.

Inclusion criteria:

- Patients aged (20-80) years who diagnosed with T2DM
- Adult diabetic patients who were prescribed Dapagliflozin as an Add-On therapy during the study period.

Exclusion criteria:

- Patients who stopped drug before 3 months period.
- Type 1 diabetes mellitus (T1DM),
- Aged <20 years,
- History of SGLT2i therapy other than dapagliflozin before the baseline,

- Pregnant woman at baseline and during the follow-up period, and
- Patient with chronic kidney disease with estimated glomerular filtration rate (eGFR) <60 ml/
- min/1.73m2.
- Patients who lost to follow-up or those who voluntarily discontinued the treatment were also excluded

Data Collection

Data of all adult diabetic patients who were prescribed Dapagliflozin as an Add-On therapy during the study period was obtained. Age, sex, duration of diabetes mellitus, fasting blood glucose, HbA1c values at the time of addition of dapagliflozin and after 3months period were collected through hospital and lab records from Department of Pharmacology. Patients who stopped drug before 3 months period were excluded. Patients who met the inclusion criteria were divided into two groups. Dapagliflozin group who had a prescription of dapaglifozin (Dapa) added to metformin (Met) ± 1 or more HGA. The control group was patients using Met ± 1 or more HGA and who didn't have any SGLT2i prescription.

Moreover, HbA1c level, glucose level, systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid profile, serum creatinine (Scr), eGFR (calculated by using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine equation), hematocrit, blood urea nitrogen (BUN), sodium, and potassium were assessed at baseline. Microalbuminuria of >30 mg/L albumin in urine were assessed at baseline and during follow-up.

Data Analysis

Collected data was entered into Microsoft excel and data was analyzed by IBM SPSS software version 29 using paired t test.

Results

Table 1: Demographic details

Gender	N%
Male	140 (70)
Female	60 (30)
Age Mean±SD	54.46 ±6.14
FBG Mean±SD	182 ±32.88
HbA1c Mean±SD	9.31 ±0.77

The mean age of patients was 54.46±6.14 years, in total 45 patients 70% (140) were male and 30% (60) were female. The mean fasting blood glucose and HbA1c levels at baseline were 9.31±0.77% and 182±32.88 respectively.

Table 2: HbA1c and FBG levels at baseline and 3 months post-treatment

Outcomemeasures	Baseline mean (SD)	At 3 monthsmean (SD)	P value
FBG	182 ±32.88	133.7±20.23	0.001
HbA1c	9.31 ±0.77	8.32± 0.92	0.001

In this study, all patients received dapagliflozin as an add-on therapy in combination with ongoing diabetic treatment. In the follow-up period, Paired T test was used to evaluate the difference in HbA1c and FBG following treatment with dapagliflozin. P values for the changes in FBG and HbA1c from baseline were significant (p=0.001 & p=0.001, respectively).

Discussion

Treatment of hyperglycemia in patients with type 2 diabetes remains a challenge, particularly in those who require insulin as

the disease progresses. [16,17] Various combinations of insulin with oral antidiabetic agents (OADs) have been investigated. [17-20] Often, these combination therapies become less effective in controlling hyperglycemia over time, particularly as a result of weight gain and worsening insulin resistance as well as progressive failure of insulin secretion. Hypoglycemia, weight gain, and subsequent increased insulin resistance are significant factors that limit optimal titration and effectiveness of insulin. [17] The 2017 American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) comprehensive glycemic control algorithm has placed SGLT2 inhibitors before DPP4 inhibitors in the hierarchical order of recommended use as monotherapy as well as add-on therapy. [21]

SGLT2 localizes almost exclusively to the kidney proximal tubules, where it reabsorbs most of the ~180 g of glucose that is filtered through the glomeruli each day. [22] In diabetic patients, the SGLT2 cotransporters are significantly upregulated, increasing glucose reabsorption and leading to glucose conservation and prolonged hyperglycemia. Dapagliflozin is a highly selective and reversible inhibitor of SGLT2 that acts by inhibiting tubular reabsorption of up to half of the glucose filtered by SGLT2 located at segments 1 and 2 in the proximal renal tubule, resulting in a dose-dependent increase in urinary glucose excretion and ultimately, an improvement in glycemic parameters. [23,24] Dapagliflozin has a different mechanism of action. By inhibiting SGLT2, dapagliflozin increases urine glucose excretion and lowers blood glucose levels by preventing the kidney's ability to reabsorb filtered glucose. Its mode of action is unrelated to insulin sensitivity and pancreatic cell activity. [23 ,25] Because of this Dapagliflozin is associated with low risk of hypoglycemia. For people who don't have better glycemic control, Dapagliflozin 'Add-On' therapy is a better and safe treatment option. According to Fioretto et al dapagliflozin is completely insulin-independent and efficacious as a single therapy or in combination with other agents.9 In another study by Jeon et al significant improvement due to addition of dapagliflozin to an existing drug regimen was noted. [26]

The mean age of patients was 54.46±6.14 years, in total 45 patients 70% (140) were male and 30% (60) were female. The mean fasting blood glucose and HbA1c levels at baseline were 9.31±0.77% and 182±32.88 respectively. In this study, all patients received dapagliflozin as an add-on therapy in combination with ongoing diabetic treatment. In the follow-up period, Paired T test was used to evaluate the difference in HbA1c and FBG following treatment with dapagliflozin. P values for the changes in FBG and HbA1c from baseline were significant ($p=0.001$ & $p=0.001$, respectively). In a study by Moustafa et al Dapagliflozin significantly reduced the HbA1c level and FBG of type 2 diabetes patients as add-on therapy, regardless of the type of the co-administered OHA or insulin. [27] In a study by Strojek et al revealed that although incidents suggestive of genital infections were recorded more frequently in patients on dapagliflozin, it was usually well tolerated and dramatically improved HbA1c in patients with uncontrolled T2DM on sulphonyl urea monotherapy. [28] These pleiotropic effects are beneficial for the prevention or reduction of macro and microvascular complications and helps in prevention and improvement of cardiovascular diseases, heart failure and chronic kidney diseases. [29, 30]

Conclusion

Dapagliflozin as an add-on therapy significantly reduced the HbA1c level and fasting blood glucose of Type-2DM patients, in a 3-month treatment period. Due to the frequency of genitourinary tract infections, caution is indicated while treating the patients.

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