ORIGINAL RESEARCH

Effectiveness of dapagliflozin in the management of type-2 diabetes mellitus in combination with other OHA's and/or insulin

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Abstract
Aim: To evaluate effectiveness of dapagliflozin in the management of type-2 diabetes mellitus in combination with other OHA's and/or insulin.
Material and Methods: This study was carried out at department of medicine, NCRIMS among 130 patients presenting with uncontrolled Type-2 Diabetes Mellitus in combination with other OHA's and/or insulin.
Results: Most of the subjects had type 2 Diabetes Mellitus from 5-10 years (53.08%), whereas rest (33.08%) had type 2 Diabetes Mellitus from > 10 years. The mean body weight among the subjects at baseline and after intervention was 71.84 kg and 68.96 kg respectively. It was found that there was significant decrease in HbA1c, FBS and PPBS value after intervention when compared to baseline values.
Conclusion: This study provides excellent real-world evidence for the early use of dapagliflozin in Indian patients with T2DM in routine clinical practice to achieve better glycemic control along with other advantages such as weight loss.
Keywords: Diabetes Mellitus, OHA, Insulin, Dapagliflozin

Introduction

Diabetes mellitus (DM) is a major public health issue affecting more than 400 million people worldwide. This metabolic disorder progressively leads to chronic microvascular, macrovascular and neuropathic life threatening complications. DM is caused either by deficiency of insulin secretion, damage of pancreatic β cell or insulin resistance related to non-use of insulin. Inclination to sedentary lifestyle may be the major reason for the continual rise in the number of diabetic patients globally which is expected to strike 366 million in 2030 in the elderly population (>65 years)[1]. Currently, most guidelines recommend pharmacologic therapy based on evaluating glycated hemoglobin (HbA1c) levels for glycemic control. When the glycemic target is not achieved by lifestyle management and metformin, a second agent may be initiated, considering medication profiles and patient-related factors. The efficacy of common antidiabetic drugs (including metformin, sulfonylureas, nonsulfonylureasecretagogues, α-glycosidase inhibitors, thiazolidinediones, glucagon-like peptide-1 analogues and dipeptidyl peptidase-4inhibitors) is insulin-dependent. Their efficacy diminishes when the function of pancreatic islet β-cells declines during the progression of type 2 diabetes mellitus (T2DM). Sulphonylureas and thiazolidinediones cause body weight gain, which further worsens insulin resistance. It came as no surprise that approximately two-thirds of the patients with diabetes in Europe and the USA under conventional treatment could not meet the goal of glycaemic control. Whereas a highly selective inhibitor of sodium glucose co-transporter 2 (SGLT2), dapagliflozin is distinctive in its insulin-independent action on reducing reabsorption of glucose particularly by the proximal tubule in the kidney to eliminate more glucose from plasma into urine[2-4].

The initiation of dual therapy should be considered in those patients who are recently diagnosed with T2DM and instead of who have HbA1c greater than or equal to 1.5% (12.5mmol/L) above their glycemic target; upgrading to triple therapy is recommended if adequate control is not achieved after 3 months. However, when glycemic control is not achieved,

range of therapeutic possibilities exist, including reversible selective sodium and glucose co-transporter 2 (SGLT2i) inhibitors, a class of drugs that inhibit glucose reabsorption in the renal proximal tubule, with a consequent glucosuric effect that decreases HbA1c, weight, and systolic blood pressure (BP). The use of these drugs in monotherapy and combination therapy produces a complementary effect that addresses several of the pathological phenomena that took place in T2DM[6,7]. Dapagliflozin efficacy is well established in clinical trials over a wide range of populations, predominantly in Western populations. However, till date, there are very few real world studies that have examined the effectiveness of this group of medications in Indian population which has a unique demographic, culture and lifestyle characteristics. The efficacy of this novel group of medications requires extensive evaluation in different populations and with different regimens to establish the best practice for managing type-2 Diabetes Mellitus. Dapagliflozin have varying effect on HBA1c, fasting blood glucose, body weight, systolic blood pressure, weight reduction, has low propensity to cause hypoglycemia and reduces the risk of cardiovascular events.

Materials And Methods

This interventional hospital based study was carried out at department of medicine, NCRIMS among patients presenting with Type-2 Diabetes Mellitus in OPD/IPD during the study period. Oral &written Informed consent was obtained from every patients for clinical examination & lab investigations.The period of study was 12 months after the approval of the research committee and the ethical committee. 130 patients of type-2 diabetes mellitus with uncontrolled diabetic status with same treatment since more than 3 months were recruited for this study.

Inclusion Criteria

1. All the patients with age more than 18 years and less than 75 years of age.
2. All previously diagnosed cases of Type 2 Diabetes Mellitus on OHAs and/or Insulin for more than 3 months.
3. Inadequately controlled Type 2 Diabetes Mellitus (HbA1c greater than 7.0% and less than 11.0%).

Exclusion Criteria

1. Patients who are newly diagnosed cases of Type 2 Diabetes Mellitus.
2. Patients with eGFR less than 45mL/min/1.73m^2 of body surface.
3. Patients taking loop diuretics.

Study Plan

In this study, all patients were receiving dapagliflozin as an add on therapy in combination with standard diabetic treatment which patient were already taking. They were divided into groups based on the most common combinations with comparable baseline readings for HbA1c and fasting blood glucose.HbA1c and FBS levels at the follow up were noted. Differences in the values of HbA1c and FBS following treatment with Dapagliflozin was evaluated at 3 month. Details about each patient's medical history, family history, clinical examination and treatment were recorded by preformed questionnaires. Data was collected and subjected to statistical analysis.

Results

The current study showed that among all the subjects 56.92% were males and 43.08% were females. Maximum subjects belonged to the age group of 50-59 years followed by > 60 years and only 6.92% subjects belonged to <40 years age group. The mean age of the subjects was 54.02±11.05 years (table 1).

Table 1: Gender and age distribution among the study subjects

Gender	N	%
Male	74	56.92
Female	56	43.08
Age Group (in years)		
<40	9	6.92
40-49	28	21.54
50-59	54	41.54
>60	39	30.00
Total	130	100

Most of the subjects had type 2 Diabetes Mellitus from 5-10 years(53.08%), whereas 33.08% had type 2 Diabetes Mellitus from >10 years. Only 13.85% had type 2 Diabetes Mellitus from 1-5 years. Out of all the subjects, 16.92% had hypertension, 10.77% had cardiovascular disease, and 6.15% had other co-morbidities (table 2).

Table 2: Duration of diabetes and co-morbidities among the study subjects

Duration	N	%
1-5	18	13.85
5-10	69	53.08
>10	43	33.08

Total	130	100
Co-morbidities		
Hypertension	22	16.92
Cardiovascular Disease	14	10.77
Other	8	6.15

There was significant decrease in weight among the study subjects after the intervention (table 3). Table 4 showed a significant comparison between the diabetic parameters of study subjects before and after the intervention.

Table 3: Comparison of body weight before and after the intervention among the study subjects

Weight (kg)	Mean	SD
Before the Intervention	71.84	5.76
After the Intervention	68.96	4.51
t test	3.62	
p value	0.042*	

*: statistically significant

Diabetic parameters among the study subjects after the intervention showed a mean HbA1c value of 7.05 ± 0.47, FBS value of 131.73 ± 6.2, and PPBS value of 204.98 ±9.42. Hence there was significant decrease in HbA1c, FBS and PPBS value after intervention when compared to baseline values (table 4).

Table 4: Comparison of diabetic parameters among the study subjects before and after the intervention

Variables	Before Intervention		After Intervention		t test	p value
	Mean	SD	Mean	SD		
HbA1c	8.31	0.56	7.05	0.47	5.08	0.009*
FBS	184.7	5.2	131.73	6.2	14.03	<0.01*
PPBS	279.25	10.83	204.98	9.42	9.58	0.005*

*: statistically significant

Discussion

Dapagliflozin, one of the seven types of SGLT2 inhibitors, is approved worldwide for the treatment of T2DM in patients who have inadequate glycemic control by conventional drugs.Dapagliflozin is currently approved in India on the basis of global studies that included a limited number of Indian patients in whom a significant decrease in the HbA1c values (-0.84% [-1.17, -0.50], P < 0.0001) was demonstrated compared with placebo after 6 months of use.[6]However, it is uncertain whether data from real-world studies of dapagliflozin will obtain similar outcomes as seen in clinical trials. To understand dapagliflozin use in routine clinical practice, we conducted this real-world study to determine the effectiveness and safety of dapagliflozin in Indian patients with T2DM. The current study showed that among all the subjects 56.92% were males and 43.08% were females. Similar findings were seen in a study done by Viswanathan V et al[7] where male predominance (57.5%) was seen among the subjects. Joaquiet al[8] showed female predominance among the subjects which is in contrast with the current findings.Maximum subjects belonged to the age group of 50-59 years followed by > 60 years and only 6.92% subjects belonged to <40 years age group. The mean age of the subjects was 54.02 years. In a study done by Joaquiet al[8] the mean age of the subjects was 55.05 years. The mean age of the subjects seen in a study done by Moustafa Al AdAwiet al[9]showed 57 years. In a study done by Viswanathan V et al[7], the mean age of patients was 52.31 years.Among all the subjects 77.77% had no family history of type 2 Diabetes Mellitus whereas 29.23% had a history of type 2 Diabetes Mellitus. The presence of a family history of diabetes may have clinical implications in risk stratification among patients who do not have a personal history of diabetes or have not yet developed diabetes. Most of the subjects had type 2 Diabetes Mellitus from 5-10 years (53.08%), whereas 33.08% had type 2 Diabetes Mellitus from > 10 years. Only 13.85% had type 2 Diabetes Mellitus from 1-5 years. In a study done by Jabbour SA et al[10] the mean duration of diabetes was 5.7 years.In a study done by Joaquiet al[8] the mean duration of type 2 Diabetes Mellitus was 5.93 years. Out of all the subjects, 16.92% had hypertension, 10.77% had cardiovascular disease, and 6.15% had other co-morbidities. In a study done by Viswanathan V et al[7]hypertension as a comorbidity was observed in 47.5% subjects.The mean body weight and height among the subjects at baseline was 71.84 ± 5.76 Kg and 162.09 ± 4.92cm respectively. The mean body weight and height among the subjects after the intervention was 68.96 ± 4.51 Kg and 162.09 ± 4.92cm respectively. In our study, a significant reduction in mean (SD) body weight of 2.88 kg was observed after 12 months of dapagliflozin treatment. Patients with higher baseline BMI showed greater body weight reductions than patients who had lower baseline BMI. Dapagliflozin had shown to produce *200–300 calorie loss per day. The greatest weight loss (between 2.2 and 3.8 kg) was

observed in the dapagliflozin add-on to metformin plus exenatide group, which had a sustained linear downward trend. These data are similar to those described in the DURATION-8 study, which showed reductions of 1 to 2.6 kg at week 28 (22) and 0.7 to 2.8 kg at week 52. Their trend was not linear; however, it did stabilize from week 28 to week 52 (23). This can be explained by the effect of GLP1 analogson weight, as they induced reductions in responders of up to 4.2 kg among diabetics (24), and up to 8 kg in non-diabetics[11].Diabetic parameters among the study subjects at baseline showed a mean HbA1c value of 8.31 ± 0.56, FBS value of 184.7 ± 5.2, and PPBS value of 279.25 ±10.83.Diabetic parameters among the study subjects after the intervention showed a mean HbA1c value of 7.05 ± 0.47, FBS value of 131.73 ± 6.2, and PPBS value of 204.98 ±9.42. This table shows a significant comparison between the diabetic parameters of study subjects before and after the intervention.Reduction in HbA1c with dapagliflozin was relatively consistent across randomized, controlled, clinical trials in a variety of settings from treatment-naive patients. The blood glucose–lowering effect of dapagliflozin after 6 months of treatment was similar to that of metformin-XR monotherapy and, after 1 year of treatment, was similar to glipizide in patients poorly controlled on metformin monotherapy.In our study, this group also had a slightly higher reduction in HbA1c and FPG when compared to the data obtained by Jabbour et al[10]. However, they reported that the percentage of patients with HbA1c <7% reached 53.9% at 28 weeks and 44% at 52 weeks (23), which is a higher proportion than reported in our results.The mean (SD) HbA1c level achieved after 6 months of dapagliflozin treatment was 7.62% (1.04%) in our patient population; this is close to the target HbA1c level (<7.0%) recommended by the American Diabetes Association[15].

Limitations

The limitations of our study include absence of an active comparator arm, which did not allow comparison with other oral antidiabetics namely glucose-dependent insulinotropic peptide-1 (GLP-1) or dipeptidyl peptidase 4 inhibitors (DPP4i). However, the large patient population ensured the generation of reliable data to accurately assess the mean change from baseline in the efficacy parameters. Still, the sample size was not large enough to describe rare AEs. This study is also limited by issues that are inherent to the real-world evidence studies, such as presence of confounders, data quality, and bias.

Conclusion

Dapagliflozin was well tolerated in patients with T2DM, and it dramatically lowered HbA1c levels and body weight after the intervention compared to baseline. The study found no new safety findings, implying that dapaglifozin has a safe tolerability profile. This trial provides excellent real-world evidence for the early use of dapagliflozin in Indian patients with T2DM in routine clinical practice to achieve better glycemic control with other advantages such as weight loss.

References

1. Roglic SWG, Green A, Sicree HR. King, Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030, Diabetes. Care 27 2004: 1047–1053.
2. Clar C, Gill JA, Court R, et al. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012; 2: e001007.
3. Chao EC, Henry RR. SGLT2 inhibition—a novel strategy for diabetes treatment. Nat Rev Drug Discov 2010; 9: 551–9.
4. Hu L, Zhou ZY. Research progress of sodium-glucose co-transporter-2 inhibitor drugs. Med Recapitulate 2011; 12: 3782–5.
5. MengW. Discovery of dapagliflozin: a potent, selective renal sodium-dependent glucose cotransporter2 (SGLT2) inhibitor forthe treatment of type 2 diabetes. *Journal of Medicinal Chemistry. 2008;* **51**(5): 1145–49.
6. Han S. Dapagliflozin, a selective SGLT2 inhibitor, improves glucose homeostasis in normal and diabetic rats. *Diabetes. 2008;* **57**(6): 1723–29.
7. Viswanathan V, Singh KP. Use of Dapagliflozin in the management of type 2 diabetes mellitus: a real-world evidence study in Indian patients (FOREFRONT). Diabetes technology & therapeutics. 2019; 21(8): 415-22.
8. Joaqui VB, Gómez NB, Ortiz RC, Toro LM, Lombo JP, Cifuentes CA, García MA, Lomba AA. Effectiveness of triple therapy with dapagliflozin add-on to dual therapy over 52 weeks in patients with uncontrolled type 2 diabetes mellitus in a centre of high complexity, Cali-Colombia. Archives of Endocrinology and Metabolism. 2021; 65: 49-59.
9. Al AdAwi RM, Jassim Z, Elgaily D, Abdelaziz H, Sree B, Mohamed Ibrahim MI. Assessment of dapagliflozin effectiveness as add-on therapy for the treatment of type 2 diabetes mellitus in a Qatari population. Scientific reports. 2019 May 3;9(1):6864.
10. Jabbour S.A, Hardy E, Sugg J, Parilh S. Dapagliflozin Is Effective as Add-on Therapy to SitagliptinWith or WithoutMetformin: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. Diabetes Care 2014; 37: 740–750.
11. Kaku K. Efficacy and safety of dapagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise. Diabetes, Obesity and Metabolism.2014; **16**(11): 1102–10.