Original Article

Safety of Empagliflozin as Add-on Therapy in Patients with Uncontrolled Type 2 Diabetes Mellitus

Mita Rani Joysoual [1], Shahin Ara [2], Sabrina Razzaque [3], Maryeum Islam [4]

Abstract

Background: *Metformin is recommended as the first-line drug for people with Type 2 Diabetes Mellitus (T2DM) who cannot achieve glycemic control by lifestyle changes. However, there are no clear recommendations for the optimal agent to combine with metformin. Empagliflozin is an effective and selective sodium-glucose co-transporter 2 (SGLT2) inhibitor that reduces blood sugar levels and can be used as monotherapy or as an add-on to existing therapy.*

Materials and Methods: *The Department of Pharmacology and Therapeutics collaborated with Rajshahi Diabetic Association General Hospital to conduct a year-long quasi-experimental study on 60 uncontrolled T2DM patients (HbA1c > 7.0 to ≤ 10.5%) for over 12 weeks. Empagliflozin 10 mg (1 tablet) was administered as a third-line medication to each patient's ongoing treatment and monitored at 6 and 12 weeks.*

Results: *The mean systolic and diastolic blood pressures decreased from 129.7 mmHg to 118.3 mmHg ($p < 0.001$) and 81.7 mmHg to 78.9 mmHg ($p = 0.03$), respectively after 12 weeks of intervention. Only one (2%) patient had suffered from UTI. The mean serum creatinine after 12 weeks of intervention was 0.8 ± 0.1 mg/dl. The additional benefit (reduction of blood pressure) may be an added advantage as many diabetics may have concurrent hypertension.*

Conclusions: *No significant incidences of UTI and hypoglycemia were seen in any patients, the drug could be considered safe.*

Key words: *Uncontrolled Type 2 Diabetes Mellitus, Add-on Therapy, Safety and Empagliflozin.*

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Introduction

Type 2 diabetes mellitus, also known as non-insulin dependent diabetes mellitus (NIDDM), is characterized by a number of pathophysiological abnormalities including islet dysfunction, decreased insulin secretion and insulin resistance.[1] Patients with Type 2 Diabetes do not require insulin on a regular basis. Insulin secretagogues, insulin sensitizers and newer drugs such as DPP-4 inhibitors are commonly prescribed in these patients. Metformin is indicated as first-line medication for T2DM patients who fail to achieve glycemic control with lifestyle changes or when this is deemed unlikely.[2] Metformin reduces hyperglycemia by decreasing gastrointestinal glucose absorption, increasing peripheral glucose uptake, improving insulin sensitivity and decreasing insulin resistance.[3] Although initially beneficial, metformin therapy alone often fails to maintain glycemic control as T2DM advances.[2, 4] When metformin alone cannot sustain glycemic control, other medications are required. Glimepiride is one of the oldest and most often used sulfonylurea drugs for the treatment of type 2 diabetes. However, long-term sulfonylurea treatment is associated with increased beta-cell dysfunction, weight gain and severe hypoglycemia.[3] Dipeptidyl peptidase 4 (DPP-4) inhibitors are advised as a second-line therapeutic option for individuals with T2DM who have not responded to metformin monotherapy.[2] However, the most commonly observed side effects (AEs) of DPP-4 inhibitors were headache, abdominal discomfort, exhaustion and nausea, along with certain alterations in blood biochemistry, which may reduce patient adherence to the treatment.[5]

Empagliflozin is a strong and specific sodium-glucose co-transporter 2 (SGLT2) inhibitor that effectively lowers blood glucose levels. Empagliflozin as a monotherapy or add-on to existing therapy was associated with clinically relevant improvements in glycemic control and weight at week 24 which were sustained until week 76, as well as reductions in blood pressure.[6, 7]

Since the first day of Empagliflozin administration, mean blood

1. Lecturer, Department of Pharmacology and Therapeutics, Rajshahi Medical College, Rajshahi, Bangladesh.
2. Professor, Department of Pharmacology and Therapeutics, TMSS Medical College, Bogura, Bangladesh.
3. Assistant Professor, Department of Dental Pharmacology, Udayan Dental College, Rajshahi, Bangladesh.
4. Assistant Professor, Department of Pharmacology and Therapeutics, Barind Medical College, Rajshahi, Bangladesh.

Corresponding author: Mita Rani Joysoual, Lecturer, Department of Pharmacology and Therapeutics, Rajshahi Medical College, Rajshahi, Bangladesh. Cell: +8801717013066, E-mail: mita.joysoual@gmail.com

glucose levels have decreased, with Empagliflozin 25 mg showing a higher reduction than Empagliflozin 10 mg.[8] Empagliflozin 10 mg and 25 mg reduced hyperglycemia (glucose ≥ 180 mg/dL) and maintained normoglycemia (glucose ≥ 70 to <180 mg/dL) with a slight increase in the risk of hypoglycemia.[9] This drug is also extremely beneficial for diabetic patients who are at high risk for cardiovascular disease, as well as individuals with Congestive Heart Failure (CHF) who require frequent diuretic medication.

Empagliflozin was well tolerated and linked to a low incidence of hypoglycemia.[7] It works by inhibiting SGLT2 in the proximal nephron which reduces glucose reabsorption and increases urine glucose excretion by up to 80 g/day.[10] Because this activity is independent of insulin, SGLT2 inhibitors can be administered at any stage of T2DM, including after insulin secretion has greatly decreased. Additional potential benefits include mild weight loss (-2 kg, stabilizing over 6-12 months) and consistent lowering of systolic and diastolic blood pressure in the range of -2 to 4/-1 to 2 mmHg.[11] This medicine is also associated with lower plasma uric acid levels and albuminuria.[12]

Furthermore, patients with T2DM at high cardiovascular risk who received Empagliflozin in the EMPA-REG OUTCOME trial had a lower rate of the primary composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and death from any cause when compared to placebo.[13] As a result, SGLT2 inhibitors are indicated as a second or third-line treatment option for T2DM patients, using a combination of SGLT2 inhibitors, DDP-4 inhibitors and metformin. The primary goal of this study is to determine the safety of Empagliflozin 10 mg as a once-daily dose for 12 weeks when used as a third-line oral hypoglycemic medication in individuals with uncontrolled diabetes.

Materials and Methods

This was a quasi-experimental study conducted from January 2021 to December 2021 at the Department of Pharmacology and Therapeutics, Rajshahi Medical College, Rajshahi, to assess the clinical outcomes of Empagliflozin 10 mg as a once-daily dose over 12 weeks when used as a third-line oral hypoglycemic agent on 60 patients with uncontrolled diabetes. The trial included adults with poorly managed T2DM (HbA1c > 7.0 to ≤ 10.5%) despite diet, exercise and stable glucose-lowering medication (Metformin combination with Sulfonylurea, DPP-4 inhibitors and/or insulin therapy) for more than 12 weeks. A systematic random sampling procedure was used to recruit the requisite number of patients who met the eligibility criteria. The researcher constructed the data collection sheet after consulting with the supervisor and examining the previously published literature. After receiving ethical clearance from Rajshahi Medical College's Institutional Review Board (IRB) and informed permission from patients (based on predetermined eligibility criteria), the study comprised 60 adult uncontrolled type 2 diabetic patients. The safety and tolerability of Empagliflozin were assessed, based on the adverse effects reported during the study period. Events consistent with hypoglycemia, urinary tract infection (UTI), genital infection, hypersensitivity reactions, pancreatitis and diabetic ketoacidosis were also recorded. Seven patients dropped out of the second follow-up from the first. All efforts were made to obtain correct data. The data was analyzed using descriptive statistics, Paired sample t-Test and the incidence of developing adverse effects (AEs) were calculated by dividing the number AEs developed during the treatment period by the number of subjects participated in the study. All statistical analysis was performed using SPSS (version 24) for Windows. The level of significance was fixed at 0.05 and p-values < 0.05 were considered significant.

Results

The mean age, duration of diabetes and BMI were 51.6 ± 10.4 years, 11.2 ± 6.4 years and 29.7 ± 7.3 Kg/m2, respectively (Table I).

Table I: Comparison of baseline variables between the two groups (n=60)

Variables	Mean±SD	Range
Mean age (Years)	51.6 ± 10.4 years	31-70 years
Mean duration of disease (Years)	11.2 ± 6.4 years	1-25 years
Mean BMI (Kg/m^2)	29.7 ± 7.3 Kg/m^2	17.5-35.9 Kg/m^2

Table II: Distribution of patients by their medications received (n = 60)

Medications received	Frequency	Percentage
Metformin + Sulfonylureas	16	26.7
Metformin + Sulfonylureas + Insulin	3	5.0
Metformin + DPP4 inhibitor	10	16.7
Metformin + DPP4 inhibitor + Insulin	17	28.3
Metformin + Insulin	7	11.7
Metformin + Sulfonylureas + DPP4 inhibitor	7	11.7

The study patients invariably received metformin. Most commonly prescribed combined antidiabetic medication was Metformin + DPP4 inhibitor + Insulin (32%), followed by Metformin + Sulfonylureas (26.7%), Metformin + DPP4 inhibitor (16.7%), Metformin + Sulfonylureas + DPP4 inhibitor (11.7%), Metformin + Insulin (11.7%) and Metformin + Sulfonylureas + Insulin (5.0%) (Table-02).

Table III: Changes in blood pressure, body-weight and BMI before and after intervention (n=53)

Variables	Level of evaluation		p - value
	At baseline	At 12 weeks of intervention	
Blood pressure			
Systolic Blood Pressure (mmHg)	129.7 ± 10.4	118.3 ± 7.5	< 0.001
Diastolic Blood Pressure (mmHg)	81.7 ± 7.9	78.9 ± 4.7	0.03
Anthropometric variables			
Body weight (kg)	71.7 ± 15.5	71.4 ± 13.0	0.874
BMI (kg/m ^{2})	29.7 ± 7.3	29.4 ± 5.1	0.752

(N.B.- Out of 60 patients 53 were considered here. Data was analyzed using Paired-sample t-Test and was presented as mean SD. p-value<.05 significant)

The mean systolic blood pressure at baseline was 129.7 mmHg which reduced to below 118.3 mmHg after 12 weeks of intervention ($p < 0.001$). Likewise, the mean diastolic blood pressure at baseline was 81.7 mmHg which decreased significantly to 78.9 mmHg at the endpoint of study ($p = 0.03$). The body weight and BMI did not change during the 12 weeks period of intervention ($p = 0.874$ and $p = 0.752$, respectively) (Table III).

Table IV: Distribution of patients by their adverse effects (AEs) (n=53)

Adverse effects (AEs)	Frequency (%)	Mean ± SD (Range)
UTI	1(2.0)	---
Serum creatinine (mg/dl)	---	0.8 ± 0.1 (0.67- 0.90)

(N.B.- Out of 60 patients 53 were considered here)

Only 1(2%) patient out of 43 exhibited events consistent with UTI. The mean serum creatinine after 12 weeks of intervention 0.8 ± 0.1 and none had over 1 mg/dl (range: 0.67-0.90 mg/dl) (Table IV).

Discussion

Type 2 diabetes mellitus (T2DM) is a chronic disease caused by insulin resistance and progressive β-cell failure. Because of the progressive nature of the disease, most of the patients with T2DM will ultimately require multiple antidiabetic agents to maintain glycemic control.

The safety and tolerability of Empagliflozin were assessed based on the adverse events reported during the study period. Events consistent with hypoglycemia, urinary tract infection (UTI), genital infection, hypersensitivity reactions, pancreatitis, and diabetic ketoacidosis were also recorded. Our study found that the mean systolic and diastolic blood pressures decreased from 129.7 mmHg to 118.3 mmHg ($p < 0.001$) and 81.7 mmHg to 78.9 mmHg ($p = 0.03$), respectively after 12 weeks of intervention. Our findings were in good agreement with Puli and Vanjari[14] and Zhong et al.[15] Puli and Vanjari[14] in a prospective study demonstrated that at 24 hours Empagliflozin significantly reduced blood pressure with mean change in SBP and DBP were -4.147 and -1.526 mmHg respectively.

Only one (2%) patient had suffered from UTI. Schorling and colleagues[16] in a recent systematic review revealed that the risk of side effects was insignificant whether patients received Empagliflozin or placebo. The mean serum creatinine after 12 weeks of intervention was 0.8 ± 0.1 mg/dl indicating that the drug was safe for kidney.

The findings of the study compared and contrasted so far with other similar studies; it is evident that Empagliflozin (10 mg) added to patients with uncontrolled Type 2 diabetes mellitus equipped them better in achieving glycemic control. However, as there was no significant incidence of UTI and there were no other adverse events or hypoglycemia, rather the drug provided additional benefit like reduction of blood pressure to the normal physiological range, the drug could be considered safe to the cardiac and renal system.

Conclusion

This study concludes that Empagliflozin as add-on therapy was safe and tolerable in patients with uncontrolled T2DM (previously treated with Metformin combined with either sulfonylurea or DPP-4 inhibitors and/or supplemented by insulin) in terms of incidence of UTI and hypoglycemia.

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References

1. Mokta JK, Ramesh, Sahai AK, Kaundal PK, Mokta K. Comparison of Safety and Efficacy of Glimepiride-Metformin and Vildagliptin- Metformin Treatment in Newly Diagnosed Type 2 Diabetic Patients. J Assoc Physicians India. 2018 Aug;66(8):30–35.

2. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun;35(6):1364-1379.

3. Kupsal K. Metformin Combinatorial Therapy for Type 2 Diabetes Mellitus. J Metabolic Synd, an open access journal. 2016 Jul;5(3):1-8.

4. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006 Dec 7;355(23):2427-2443.

5. Tang Y-Z, Wang G, Jiang Z-H, Yan T-T, Chen Y-J, Yang M, et al. Efficacy and safety of vildagliptin, sitagliptin, and linagliptin as add-on therapy in Chinese patients with T2DM inadequately controlled with dual combination of insulin and traditional oral hypoglycemic agent. Diabetol Metab Syndr. 2015 Oct 19;7(1):91.

6. Kovacs CS, Seshiah V, Merker L, Christiansen AV, Roux F, Salsali A, et al. Empagliflozin as Add-on Therapy to Pioglitazone With or Without Metformin in Patients With Type 2 Diabetes Mellitus. Clin Ther. 2015 Aug;37(8):1773-88.e1.

7. Roden M, Merker L, Christiansen AV, Roux F, Salsali A, Kim G, et al. Safety, tolerability and effects on cardiometabolic risk factors of empagliflozin monotherapy in drug-naïve patients with type 2 diabetes: a double-blind extension of a Phase III randomized controlled trial. Cardiovasc Diabetol. 2015 Dec 23;14(1):154.

8. Nishimura R, Tanaka Y, Koiwai K, Inoue K, Hach T, Salsali A, et al. Effect of empagliflozin monotherapy on postprandial glucose and 24-hour glucose variability in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, 4-week study. Cardiovasc Diabetol. 2015 Jan 30;14:11.

9. Tanaka A, Inoue T, Kitakaze M, Oyama J-I, Sata M, Taguchi I, et al. Rationale and design of a randomized trial to test the safety and non-inferiority of canagliflozin in patients with diabetes with chronic heart failure: the CANDLE trial. Cardiovasc Diabetol. 2016 Apr 4;15:57.

10. Bakris GL, Fonseca VA, Sharma K, Wright EM. Renal sodium-glucose transport: role in diabetes mellitus and potential clinical implications. Kidney Int. 2009 Jun;75(12):1272-1277.

11. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013 Aug 20;159(4):262-274.

12. Chino Y, Samukawa Y, Sakai S, Nakai Y, Yamaguchi J, Nakanishi T, et al. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. Biopharm Drug Dispos. 2014 Oct;35(7):391-404.

13. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-2128.

14. Puli K, Vanjari NK. A 12 week prospective clinical evidence of empagliflozin efficacy in uncontrolled type 2 diabetes mellitus treated with metformin and a sulfonylurea. Int J Basic Clin Pharmacol. 2019 Nov 25;8(12):2639.

15. Zhong X, Lai D, Ye Y, Yang X, Yu B, Huang Y. Efficacy and safety of empagliflozin as add-on to metformin for type 2 diabetes: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2016 Jun;72(6):655-663.

16. Kinduryte Schorling O, Clark D, Zwiener I, Kaspers S, Lee J, Iliev H. Pooled Safety and Tolerability Analysis of Empagliflozin in Patients with Type 2 Diabetes Mellitus. Adv Ther. 2020 May; 37(8):3463-3484.