EFFICACY AND SAFETY OF EMPAGLIFLOZIN AS ADD-ON THERAPY IN PATIENTS OF TYPE-2 DIABETES MELLITUS

Nauman Wazir[1], Shafqat Ur Rehman[2]

ABSTRACT:

OBJECTIVES:

To assess efficacy of two doses i.e., 10 mg and 25 mg in lowering the glycated haemoglobin (HbA1C) and fasting blood glucose (FBG) in patients of type 2 diabetes mellitus (T2DM) having suboptimal glycaemic control on maximal doses of Metformin and Sitagliptin, and to see the frequency of its side-effects.

***METHODOLOGY**:*

The study design was a randomized control trial. Fifty nine adult patients of T2DM who were already on 2000 mg of Metformin and 100 mg of Sitagliptin and were having suboptimal glycaemic control (HBA1C >7% and <12%) were randomized to two groups, one group receiving 10 mg (Group A) and the other group receiving 25 mg of empagliflozin (Group B) as an additional treatment. HbA1C and FBG were taken before and 12 weeks after addition of empagliflozin in both the groups. Side effects of empagliflozin such as urinary tract infections (UTI) and genital mycotic infections were also recorded in both the groups.

***RESULTS**:*

Total patients in-group A were 31 and their mean age was 51.48±4.29 years. In-group B there were 28 patients and their mean age was 52.39±5.20 years. There was a statistically significant reduction of both HbA1C and FBG in both the groups after empagliflozin treatment; (p=0.000) for both HbA1C and FBG in both the groups. Although numerically UTI and genital mycotic infections were more than pre-treatment numbers, they were not statistically significant (p>0.05).

CONCLUSION:

Empagliflozin can be safely added to the oral anti-diabetic regimen of patients with type 2 diabetes mellitus who have suboptimal glycaemic control and results in significant improvement in HbA1C.

***KEYWORDS**: Empagliflozin, Type-2 Diabetes Mellitus, Glycated Haemoglobin*

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Correspondence
[1]Nauman Wazir, Locum Consultant Physician in Diabetes and Endocrinology, William Harvey Hospital, East Kent University Hospitals Foundation NHS Trust. UK
+44-79276598-6
Nauman.wazir@yahoo.com
[2]Assistant Professor, Department of Medicine, Naseer Teaching hospital, Peshawar

INTRODUCTION:

Metformin is advocated and used as first-line treatment to attain glycaemic control in patients with T2DM. However, metformin monotherapy may usually not provide sustained glycaemic control for a long time[1], and additional treatments are often required in most patients[2]. Although they appear to be effective in attaining glycaemic control at first, sulfonylureas and oral hypoglycaemic agents are

difficult to tolerate in the long run due to their side effects[3]. Hence, patients with T2DM need new anti-diabetic agents that are both effective and well tolerated, and can be used in combination with other available treatment options to improve overall glycaemic control, without the added risk of hypoglycaemia and weight gain. The sodium glucose co-transporter 2 (SGLT2) is located in the proximal tubule of the kidney and is responsible for approximately 90% reabsorption of the filtered glucose[4]. Due to maladaptive enhanced expression of SGLT2 in patients with T2DM, the capacity of the kidneys for reabsorption of glucose is increased, which further deteriorates hyperglycemia[4]. Sodium-glucose co-transporter 2 inhibitors (SGLT2-I) form a new class of oral anti-diabetic drugs for the treatment of diabetes. They act by reducing renal glucose reabsorption and thus increasing urinary glucose excretion,[5] resulting in reduced hyperglycaemia. SGLT2-I can be used as combination therapy with metformin, dipeptidyl peptidase 4 inhibitors (DPP-4), thiazolidinediones, sulfonylurea (SU) or other anti-diabetic agents, including insulin[6-8]. As their mechanism of action is independent of insulin, they can be used in appropriate candidates at any stage of diabetes. SGLT2-I is recommended as one of the second-line treatment options by the American Diabetes Association (ADA) and the European Association for the study of Diabetes (EASD)[9]. Empagliflozin is a potent sodium-glucose co-transporter-2 inhibitor utilized in the treatment of T2DM that has more than 2500-fold affinity for SGLT-2 over SGLT-1[10]. This study was aimed to assess the efficacy and safety of two doses of empagliflozin (10 and 25 mg) when added to on-going dual oral anti-diabetic treatment (metformin plus sitagliptin) in patients with suboptimal glycaemic control.

METHODOLOGY:

This study was conducted between January 2020 and December 2020, at the department of Medicine, Naseer Teaching Hospital, Peshawar. Ethical approval was sought from the Institutional Review and Ethics Board of Naseer Teaching Hospital, Peshawar, which was provided. Consecutive patients who were previously diagnosed to have T2DM and did not achieve optimal glycaemic control (HbA1C of >7% and <12%) with Metformin 2000 mg daily and Sitagliptin 100 mg daily were included in the study. Other inclusion criteria were age more than 18 years and both genders. Exclusion criteria were patients with impaired renal function (estimated Glomerular Filtration rate of <45ml/), pregnancy, chronic liver disease, cerebrovascular event or acute coronary syndrome. A total of 84 patients met the inclusion criteria of which 7 were excluded as per the exclusion criteria and rest (seventy six) were included in the study. These were randomized to two groups of interventions by lottery method. Group A received empagliflozin 10 mg on top of the previous treatment and group B received empagliflozin 25 mg in addition to the previous treatment. Both the groups were followed up for 12 weeks during the study duration of 1 year. Seven patients of group A and 10 patients of group B were lost to follow up. Therefore at the end of study duration had the follow up data of a total of 59 patients (31 in group A and 28 in group B). Fasting blood glucose and HbA1c were obtained before and 12 weeks after intervention with empagliflozin treatment. The SPSS 23.0 version was used to analyse the data. Mean±SD were calculated for quantitative variables like age, HbA1c and FBG. Percentages and frequency were calculated for qualitative variables like gender and presence of side effects. Analysis was done by doing paired sample t-tests to determine group mean differences between descriptive variables of the two intervention groups at 12 weeks and at baseline. To see the difference of outcome between the two intervention groups, an independent sample t-test was used. Side effects i.e. urinary tract infections and genital mycotic infections of both groups were compared to the baseline by using Fisher Exact t-test. A value for p-value <0.05 was considered statistically significant.

RESULTS:

A total of 59 patients (29 males and 30 females) were included in the study. In Group A there were a total of 31 patients, out of which 13 patients were male and 18 were female, and the mean age was 51.48±4.29 years. In Group B, there were a total of 28 patients, out of which 16 patients were male and 12 were female, and the mean age was 52.39±5.20 years. The clinical and demographic variables of Group A and Group B are depicted in Table 1 and 2, respectively. The between group difference is shown in Table 3.

Parameter	Baseline	Group A	P-Value
Age (Years)	51.48±4.29		
Gender (Male/Female, %)	13 (41.9%) / 18 (51.9%)		
Duration of Diabetes, Years (SD)	6.5±2.3		
HbA1C, % (SD)	10.11±0.79	8.67±1.03	0.000
FPG, mg/dl (SD)	205.45±14.31	165.54±16.31	0.000
UTI (%)	1	2	0.935
Mycotic Infections (%)	1	3	0.893

*HbA1C=Glycated haemoglobin, FPG=Fasting plasma glucose, UTI=Urinary tract infections

Table 2: Clinical and Demographic Data in Patients Receiving Empagliflozin Treatment in Group B

Parameter	Baseline	Group B	P-Value
Age (Years)	52.39±5.20		
Gender (Male/Female, %)	16 (57.1%) / 12 (42.9%)		
Duration of Diabetes, Years (SD)	6.8±2.5		
HbA1C, % (SD)	9.39±0.56	8.32±0.76	0.000
FPG, mg/dl (SD)	215.39±20.17	175.82±20.48	0.000
UTI (%)	1	2	0.929
Mycotic Infections (%)	1	2	0.929

*HbA1C=Glycated haemoglobin, FPG=Fasting plasma glucose, UTI=Urinary tract infections

Table 3: Comparison of Pre and Post Added Empagliflozin Therapy Differences in Parameters Between Group A and Group B

Parameter	Change from Baseline Treatment		P-Value
	Group A	Group B	
Δ FPG, mg/dl (SD)	-39.90±10.58	-39.57±12.46	0.91
Δ HbA1C, % (SD)	-1.43±0.79	-1.06±0.61	0.047

DISCUSSION:

Our study showed that the addition of either doses of empagliflozin as a further treatment option to T2DM patients having suboptimal glycaemic control already receiving Sitagliptin plus Metformin resulted in a significant HbA1c decline. Similar trend was also seen in the mean fasting plasma glucose (FPG) level decline after 12 weeks intervention in both the groups. This result of our study is in line with the results of numerous international studies[6, 11-16]. Recently, a study from Karachi has also demonstrated efficacy of empagliflozin in improvement of HbA1C levels in Pakistani population[17]. Unexpectedly, the in-between group differences showed a higher HbA1C decline in empagliflozin 10 mg intervention group as compared to empagliflozin 25 mg group {-1.43±0.79% vs -1.06±0.61 (p=0.047)}. This might be attributed to a high baseline HbA1C level in the empagliflozin 10 mg group. This contrasts with dose dependent decrease in HbA1C values as shown by Ferrannini et al[18]. Their study showed that after 12 weeks there was a 0.5 % decrease in the group receiving 10 mg while 0.6 % decrease in those receiving 25 mg of empagliflozin. However, there was no statistically significant difference in the mean FBG decline between both the groups. Both the doses of empagliflozin appeared quite safe. Although there was a numerically increased number of urinary tract infections (UTI) and genital mycotic infections in both the groups, these were not statistically significant.

LIMITATIONS:

A relatively small sample size and short duration of follow up are potential limitations of this study.

CONCLUSION:

Empagliflozin can be safely added to the oral anti-diabetic regimen of patients with type-2 diabetes mellitus who have suboptimal glycaemic control and results in significant HbA1C reduction and a low side-effects rate.

CONFLICT OF INTEREST: None

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CONTRIBUTORS

1. **Nauman Wazir -** Concept & Design; Data Analysis/Interpretation; Drafting Manuscript; Final Approval
2. **Shafqat Ur Rehman -** Data Acquisition; Critical Revision; Supervision