ORIGINAL ARTICLE

COMPARISON OF EFFICACY AND SAFETY PROFILE OF EMPAGLIFLOZIN AS A COMBINATION THERAPY IN OBESE TYPE 2 DIABETIC PATIENTS

Muhammad Babar[1], Mazhar Hussain, Manzur Ahmad[2], Lubna Akhtar[2]
[1]Department of Medicine, [2]Department of Pharmacology, Sheikh Zayed Medical College and Hospital, Rahim Yar Khan-Pakistan

Background: Type 2 diabetes mellitus (T2DM) is a progressive disease due to multiple pathophysiological defects. Monotherapy alone cannot achieve adequate glycemic control and can lead to treatment failure. Empagliflozin, a sodium-glucose cotransporter2 (SGLT2) inhibitor improves glycemic control in patients with T2DM. There were limited studies to determine efficacy and safety profile of empagliflozin with conventional oral antidiabetic drugs (OADs) in Pakistan. So we investigated the efficacy and safety profile of empagliflozin as add-on therapy to metformin and sitagliptin in T2DM patients. **Methods:** In this comparative randomized placebo-controlled trial, 240 obese type 2 diabetic patients with inadequate glycaemic control (i.e, HbA1c ≥7%) with metformin and sitagliptin were allocated in to two groups. Patients in group B were given tab empagliflozin 10mg twice a day while patients in group A were given tab placebo for a period of 24 weeks. Changes in body weight, HbA1c, blood pressure were analysed pre and post treatment by using SPSS v23. **Results:** Empagliflozin caused a significant reduction in body weight -6.9±2.4 kg as compared to placebo -3.1±0.8 kg with *p*-value <0.001. This body weight reduction was further accompanied by reduction in systolic blood pressure -10.1±2.6 mmHg in empagliflozin group versus -5.3±2.5 mmHg in placebo group with *p*-value <0.001, and HbA1c -1.68±0.45 in empagliflozin group versus -0.1±0.06 in placebo group with *p*-value <0.001. There were 28.3% patients in empagliflozin group in whom HbA1c levels reduced <7% as compared to only 13.3% patients in placebo group (*p*-value 0.04). However no significant adverse effects were recorded in both study groups. **Conclusion:** Empagliflozin as a combination therapy has good efficacy and safety profile in obese type 2 diabetic patients.

Keywords: Type 2 diabetes mellitus; Metformin; Empagliflozin; HbA1c

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INTRODUCTION

Traditionally Type 2 diabetes mellitus (T2DM) has been managed by step wise approach from life style modifications to metformin as first line drug-based therapy, then use of combination drugs if not properly controlled by metformin and ultimately insulin therapy.[1] Availability of modern treatment options have greatly reduced the complications of T2DM but mortality rate is still high in these patients as compared to healthy population.[2,3]

In patients taking monotherapy with metformin, haemoglobin A1c (HbA1c) levels increase very steadily resulting in requirement of additional therapy to maintain HbA1c level in normal limits.[4,5] There is a difference in current guidelines about the time to start combination therapy. Some guidelines suggest to start combination therapy if HbA1c increased >1.5% of the targeted control value[6], while others recommend to start combination therapy when HbA1c >7.5%[7]. The main reason for starting combination therapy is that combination therapy provides faster improvement of glycaemic control and avoids clinical inertia.[8,9]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have gained popularity as initial combination therapeutic option along with metformin. SGLT2 inhibitors did not act directly to control blood sugar levels, they increase glucose excretion in urine and thereby lower blood sugar levels.[10] The use of SGLT2 inhibitors have several benefits; by increasing urinary glucose excretion without the use of insulin they lower workload on pancreatic β-cells, if blood sugar level falls excretion in urine will decrease thereby preventing the risk of severe hypoglycaemia, sodium excretion along with glucose by sodium-glucose cotransporter 2 (SGLT2) inhibitors in urine may also lower blood pressure, and it can also lower body weight.[11–13]

In present study we compared the effectiveness and adverse events of SGLT2 inhibitors (empagliflozin) as combination therapy for management of type 2 diabetes mellitus.

MATERIAL AND METHODS

This randomized placebo-controlled trial was conducted in the department of medicine Sheikh

Zayed Medical College/hospital Rahim Yar Khan. We included 240 patients in this study from Jan-2018 to Feb-2019.Adult patients of age ≥18 years having T2DM, body mass index ≥35 Kg/$m^2$and who were taking stable dose of metformin (1500 mg/day) and sitagliptin 100 mg/day for ≥12 weeks with inadequate glycaemic control (i.e., HbA1c≥7%). Patients with serum creatinine (S Cr) ≥1.3 mg/dl, having symptoms of poor diabetes control such as polydipsia or polyuria, those with coronary heart disease were excluded. Written consent was taken from each patient for inclusion in study.

Before randomization the patients were taking metformin 750 mg plus sitagliptin 50 mg twice a day. Patients were divided into two groups using draw randomization. In group B patients, metformin 1500 mg daily plus empagliflozin 10 mg twice a day was given. While in group A; metformin 1500 mg daily plus tab placebo was given for the required period of time. Sitagliptin was continued at the dose of 50 mg twice a day in both groups. The treatment duration was 24 weeks. Rescue medications were advised if patients fasting blood sugar (FBS) were >140 mg/dL. In case of hypoglycaemia the dose of rescue medications reduced or totally discontinued. The primary study point was changes in body weight, blood pressure and HbA1c while secondary end points were to observe any adverse effects after 24 weeks therapy. Data analysis was performed by using SPSS v23 software. HbA1c levels, hemodynamic profile and weight of patients were compared using un-paired sample t-test for continuous variables. While Chi-square test was used for comparison of qualitative variables. *p*-value ≤0.05 was taken as significant difference.

RESULTS

There were no significant differences in age, sex, duration of diabetes, body weight, HbA1c, systolic blood pressure (SBP) and diastolic blood pressure (DBP) at baseline in both study groups. These baseline characteristics of both study groups have shown in table-1. There were 31.7% whose HbA1c levels were ≥8.5% in placebo group versus 35% in empagliflozin group (Table-1).

Regarding efficacy of empagliflozin, we found significant reduction in mean HbA1c levels in empagliflozin group, -1.68±0.45 versus -0.1±0.06 in placebo group (*p*-value <0.001). There were 28.3% patients in empagliflozn group in whom HbA1c levels reduced <7% as compared to only 13.3% patients in placebo group (*p*-value 0.04). Similarly, we also found significant reduction in SBP, DBP and mean weight of patients after 24 weeks of treatment. Weight reduction was -3.1±0.8 kg in placebo group versus -6.9±2.4 kg in empagliflozin group (*p*-value <0.001).

Hypoglycaemia was occurred in 6 (5.0%) patients in placebo group versus in 8 (6.7%) patients in empagliflozin group. Hyperglycaemia occurred in 30 (25%) patients in placebo and in only 14 (11.7%) patients in empagliflozin group (*p*-value 0.05). Urinary tract infections occurred in 10(8.3%) patients in placebo versus in 12 (10%) patients in empagliflozin group (Table-2).

Table-1: Baseline characteristics

	Group A (Placebo) (n=120)	Group B (Empagliflozin) (n=120)	*p*-value
Age	52.53±8.6	53.4±9.1	0.59
Male Gender	106 (88.3%)	110 (91.7%)	0.54
Time of Diagnosis of T2DM			
≤1 Years	12 (10%)	8 (6.6%)	0.75
1–5 Years	38 (31.6%)	48(40%)	
5–10 Years	46 (38.3%)	44(36.7%)	
>10 Years	24 (20%)	20 (16.7%)	
HbA1c %	8.0±0.7	7.9±0.9	0.49
HbA1c (N, %)			
<8.5%	82 (68.3%)	78 (65%)	0.69
≥8.5%	38(31.7%)	42 (35%)	
Body Weight	73.8±17.21	74.5±18.04	0.99
SBP	127.8±15.2	128.3±14.8	0.85
DPB	80.8±6.9	79.5±7.4	0.32

SBP: Systolic blood pressure, DBP: Diastolic blood pressure)

Table-2: Comparison of study outcomes

	Group A (Placebo)	Group B (Empagliflozin)	*p*-value
Change in HbA1c levels	-0.1±0.06	-1.68±0.45	<0.001
Reduction of HbA1c <7%	8(13.3 %)	17 (28.3 %)	0.04
Change in SBP	-5.3±2.5	-10.1±2.6	<0.001
Change in DBP	-4.1±1.3	-8.5±4.2	<0.001
Mean change in Body Weight	-3.1±0.8	-6.9±2.4	<0.001
Adverse Events			
Hypoglycaemia	6(5.0 %)	8 (6.7 %)	0.69
Hyperglycaemia	30 (25%)	14 (11.7%)	0.05
UTI	10(8.3%)	12 (10%)	0.75

DISCUSSION

In present study we evaluated the efficacy and safety of empagliflozin as an add-on therapy. We found that addition of empagliflozin 10 mg twice a day for 24 weeks has a significant efficacy in controlling the HbA1c levels and returning HbA1c levels back to normal limits. All of our patients were having HbA1c levels more than 7 at the time of enrolment. HbA1c reduced to -1.68±0.45 in empagliflozin group versus -0.1±0.06 in placebo group with *p*-value <0.001. There were 28.3% patients in empagliflozin group in whom HbA1c levels reduced <7% as compared to only 13.3% patients in placebo group (*p*-value 0.04) after 24 weeks of treatment.

Hadjadj *et al*. in a study on 1364 patients of T2DM and divided them into 7 groups using different combinations of empagliflozin with metformin and metformin alone. The authors reported significant reductions in HbA1c levels -1.9 to -2.1% using empagliflozin with metformin using b.i.d treatment, and -1.4% using once daily regimens, and -1.2% to -1.8% using metformin b.i.d and empagliflozin OD treatment. The authors concluded that reduction in HbA1c levels was more using b.i.d. regimens as compared to empagliflozin OD with metformin b.i.d. These authors took 5 mg empagliflozin to 25 mg of empagliflozin from OD to b.i.d. They reported weight reduction of -2.8 to -3.8% in b.i.d treatment group as compared to -0.5 to -1.3 kg in metformin only group with significant difference.[14]

Another study by Søfteland *et al*. on 24 weeks' treatment of empagliflozin (10 mg and 25 mg) with metformin and compared it with placebo management. The authors also reported a significant reduction in HbA1c levels from baseline value, -0.79% in empagliflozin in 10 mg group, -0.70% in 25 mg empagliflozin group versus -0.46% in placebo group. The authors reported adverse events in 68.2% patients who received placebo group, 55.4% patients who received 10 mg empagliflozin and in 51.8% patients receiving 51.8% patients receiving 25 mg empagliflozin.[15]

Another study by Haring *et al*. also reported similar results. They also found significant reduction in systolic blood pressure, -0.4±0.7% in placebo group, and -4.5±0.7% in patients who received empagliflozin 10 mg and -5.2±0.7% in patients who received 25 mg empagliflozin. They reported similar changes in diastolic blood pressure ae well. They also reported reduction in body weight, the weight reduction was maximum in patients receiving 25 mg empagliflozin and minimum in control group.[16] Merker *et al*. also reported similar outcomes.[17]

In present study, mean SBP reduction was -5.3±2.5 mmHg in placebo group versus -10.1±2.6 mmHg in study group (*p*-value <0.001). While mean reduction in DBP was -4.1±1.3 mmHg in placebo group versus -8.5±4.2 mmHg in study group (*p*-value <0.001).

CONCLUSION

Empagliflozin as a combination therapy has good efficacy and safety profile in obese type 2 diabetic patients. It can be used in newly diagnosed obese type 2 diabetic patients with in adequate glycaemic control with other anti-diabetic medications.

Future Recommendation: Further trial on empagliflozin should be conducted in Pakistan in order to determine its cardiovascular and renal safety as done in other countries.

AUTHORS' CONTRIBUTION

MB: Conceived the idea, manuscript review and statistical analysis. MH: Designed the study, preparing the manuscript and data analysis. MA: Search the literature, collected the clinical data and manuscript editing LA: Interpreted the data with final editing and drafting of manuscript. All members hereby agree to take responsibility of the work and confirm that all questions related to the accuracy and integrity of the research has been properly and thoroughly resolved.

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Address for Correspondence:

Dr. Mazhar Hussain, House No 214/C, Satellite Town, Rahim Yar Khan-Pakistan
Cell: +92 321 672 3330
Email: mazharhussain214@gmail.com