

EFFICACY AND SAFETY OF ADDITION OF EMPAGLIFLOZIN IN DIABETIC PATIENTS UNCONTROLLED WITH GLIMEPIRIDE + METFORMIN + TENELIGLIPTIN

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ABSTRACT

BACKGROUND

The aim of this study was to evaluate the efficacy and safety of empagliflozin as an add-on drug in type 2 diabetes mellitus (T2DM) patients demonstrating inadequate disease control to triple drug treatment of glimepiride, metformin and teneligliptin.

MATERIALS AND METHODS

The prospective, observational study, conducted in a clinical setting, included subjects with T2DM, aged between 40-70 years, with inadequate disease control to triple drug treatment (glimepiride, metformin and teneligliptin) and glycated haemoglobin (HbA1c) of >7.5%. Clinical parameters such as serum creatinine, urea, HbA1c, fasting and postprandial blood sugar levels, and weight was measured before and after the study. The pre-and post- anthropometric and laboratory parameters were compared using paired t-test and Wilcoxon signed-rank test.

RESULTS

The study included 41 subjects with a mean age and disease duration of 58±5.13 years and 5±2.10 years respectively. Fasting and postprandial blood sugar levels, weight and HbA1c% of the subjects following treatment showed significant ($P < 0.0001$) improvement from the pre-treatment values. The HbA1c% was <0.7% in 46.34% (n=19) of the subjects, and 53.66% (n=22) of the subjects achieved HbA1c >0.7% reduction. Adverse reactions noted in the subjects included mild hypoglycaemia, urinary tract infection and mycotic infection.

CONCLUSION

Empagliflozin can provide significant clinical benefits for T2DM patients, showing inadequate control to triple drug treatment of metformin, glimepiride and teneligliptin.

KEYWORDS

Empagliflozin, T2DM, HbA1c, Triple Drug Treatment, Hypoglycaemia.

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BACKGROUND

Over the past decades, diabetes mellitus (DM) has emerged as one among the most prevalent chronic diseases associated with high mortality rate globally.¹ As per the latest World Health Organization fact sheet (2016), diabetes burden has increased from 108 million in 1980 to over 422 million by 2014, with more rapid rise in low- and middle-income countries.^{1,2} According to the International Diabetes Federation, the global disease burden is projected to reach 552 million by 2030.³ The 2015 data shows that around 69.2 million Indians are living with diabetes.⁴ T2DM accounts for 90-95% of all diagnosed cases of DM, causing around 5 million deaths per year.^{5,6}

Triple drug therapy of varying doses has been introduced in India following the global acceptance of two

drug fixed combinations.⁷ Several studies employing triple drug treatment for T2DM patients have shown that the therapy provides clinically relevant reduction in HbA1c levels.⁸ However, there is no specific recommendations on how to manage patients not showing adequate control with triple drug therapy, apart from transitioning to insulin.⁹ Reluctance in beginning injectable insulin therapy has been noted in many of the patients owing to misconception and inadequate knowledge regarding the treatment.¹⁰

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are among the recently approved medication for hyperglycemia.¹¹ The primary mode of action of these drugs involves the inhibition of SGLT2 in the proximal convoluted tube, thereby facilitating the urinary excretion of glucose by preventing its reabsorption.¹² SGLT2 inhibitors works parallel with blood glucose levels, hence the risk of increased hypoglycaemia is minimal and the chances of overstimulation of beta cells are scarce.¹²

Empagliflozin, a potent and competitive SGLT2 inhibitor, is a well-tolerated drug in T2DM patients.¹³⁻¹⁵ The drug has gained US FDA in August 2014 to reduce T2DM associated cardiovascular risk in adult patients.¹⁶ Central Drug Standards Control Organization has approved the drug in India at 10mg and 25 mg doses on May 2015, to improve

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glycaemic control in adults with T2DM.¹⁷ T2DM patients undergoing phase II and III clinical trials with empagliflozin exhibited good safety profile and pronounced improvement in the levels of HbA1c, during monotherapy and with metformin. The drug, which enables dose-dependent urinary glucose excretion, is associated with additional benefits of reduction in insulin dose, weight loss and reduction in systolic blood pressure.¹⁴ The safety of the drug has been proven for effectively reducing HbA1c levels in patients with 2nd or 3rd stage chronic kidney disease.¹³ In addition, the drug has been demonstrated to significantly reduce the incidence of cardiovascular diseases in T2DM patients.^{18,19}

Gupta et al. (2017) have demonstrated the long-term tolerability, sustained glycemic efficacy and safety of empagliflozin monotherapy in drug-naïve Indian T2DM patients.^{20, 21} However, literature evidence from national and international studies on the efficacy and safety of empagliflozin, as an add-on to triple drug treatment, is very limited. The present study was conducted to evaluate the efficacy and safety of addition of empagliflozin (25 mg/day) in T2DM patients with inadequate disease control to triple drug treatment: glimepiride, metformin and teneligliptin.

MATERIALS AND METHODS

The prospective observational study included subjects attending a clinical setting from June 2016 to Dec 2017. Informed consent was obtained from all the participants. The study included subjects, aged between 40-70 years, showing inadequate disease control to triple treatment; glimepiride (8 mg/day), metformin (2 g/day) and teneligliptin (20 mg/day) with glycated haemoglobin (HbA1c) of >7.5%. Subjects with serious complications such as significant osmotic symptoms, pneumonia and acute myocardial infarction were excluded from the study. Demographic and clinical characteristics such as age, sex, height, weight, duration of DM etc. were obtained from all the subjects. All the subjects received empagliflozin at a dose of 25 mg/day, along with the triple drug treatment of glimepiride (8 mg/day), metformin (2 g/day) and teneligliptin (20 mg/day) for a period of three months. Urea, weight, serum creatinine, HbA1c and fasting and postprandial blood sugar levels were measured before and after the study. Fasting and postprandial plasma glucose levels and glycated haemoglobin (HbA1c) levels were measured. The outcome measures considered were incidence of adverse drug reactions and changes in postprandial plasma glucose and HbA1c over time from baseline.

Statistics

Comparison of pre- and post-anthropometric and laboratory parameters was performed by paired t-test for normal data and Wilcoxon signed-rank test for data without normal distribution. P value <0.05 was considered as statistically significant. The pre- and post-study data was compared and quantified as increased, stable/remained unchanged or decreased based on the delta analysis. Percent reduction in HbA1c of 0.3%, 0.7% and 1% were verified as prespecified

end-points.²² All the statistical analyses were performed using Medcalc software version 14.8.1 (MedCalc Software, Ostend, Belgium).

RESULTS

Out of the 54 enrolled subjects with T2DM, 13 were excluded due to serious complications. The study included 41 subjects with a male to female ratio of 1:0.7. The mean(SD) age of the participants was 58(5.13) years and the mean disease duration noted was 5(2.10) years. The descriptive details of demographic and anthropometric measures of the subjects are provided in table 1.

Parameters	Values
Age (yrs.)	57.78 ± 5.13
Gender (M/F)	24/17
Duration of DM (yrs.)	5.36 ± 2.10
Height (cm)	163.93 ± 4.03

Table 1. Descriptive Statistics for Demographic and Anthropometric Variables of the Subjects

The comparison of variables before and after the treatment showed that the average body weight, blood sugar (fasting and postprandial) and HbA1c values of the subjects significantly (P <0.0001) improved after the study. The fasting and postprandial blood sugar levels of first, second and third month also showed statistically significant difference (P <0.0001) from the pre-study values. However, no statistically significant difference was noted for serum urea (P 0.1403) and creatinine (P 0.2641) (Table 2).

Factors	Pre-study (n=41)	Post study (n=41)	P value
Body weight (kg)	63.88 ± 5.22	62.78 ± 5.19	< 0.0001
Serum urea (mg/dL)	22.8 ± 5	22.1 ± 5.22	0.1403
Serum creatinine (mg/dL)	0.98 ± 0.19	1.04 ± 0.28	0.2641
Fasting Blood Sugar (mg/dL)			
One month	166.66 ± 19.55	164.07 ± 201.05	< 0.0001
Two months	166.66 ± 19.55	120.58 ± 25.22	< 0.0001
Three months	166.66 ± 19.55	112.39 ± 25.47	< 0.0001
Postprandial Blood Sugar (mg/dL)			
One month	274.46 ± 40.46	210.97 ± 39.60	< 0.0001
Two months	274.46 ± 40.46	196.49 ± 41.90	< 0.0001
Three months	274.46 ± 40.46	188.63 ± 42.19	< 0.0001
HbA1c (%)	7.89 ± 0.55	7.14 ± 0.68	< 0.0001

Table 2. Comparison of Pre- and Post-Study Levels of Anthropometric and Laboratory Parameters in the Study Subjects

Following the treatment, all the subjects achieved decrease in the levels of HbA1c%, fasting blood sugar and postprandial blood sugar as indicated by delta analysis (Table 3). Body weight decreased in 27 subjects, increased in 5 subjects and remained stable in 9 subjects. Similarly, serum urea and creatinine were decreased in 22 and 12 subjects respectively.

Percentage reduction in pre-specified HbA1c cut-off levels showed that 6 patients achieved $\leq 0.3\%$, 13 patients $>0.3\%$ to $\leq 0.7\%$, 13 patients $>0.7\%$ to $\leq 1.0\%$, and 9 patients $>1\%$. Overall, 46.34% (n=19) of the subjects achieved HbA1c levels $<0.7\%$ and 53.66% (n=22) of the subjects $>0.7\%$.

Factors	Number of subjects		
	Increased	Decreased	Stable
Body weight	5	27	9
Serum urea	18	22	1
Serum creatinine	21	12	8
Fasting blood sugar			
One month	1	40	0
Two months	1	40	0
Three months	0	41	0
Postprandial blood sugar			
One month	1	40	0
Two months	1	40	0
Three months	0	41	0
HbA1c	0	41	0

Table 3. Post-Study Delta Difference in Clinical and Laboratory Parameters of the Subjects

There was no drop out due to adverse reactions such as deterioration of renal function, complications related to osmotic diuresis, volume depletion, diabetic ketoacidosis and amputation. Adverse reactions noted were mild hypoglycemia, urinary tract infection (8% males and 14% females) and mycotic infection (14% males and 17% females).

DISCUSSION

Empagliflozin, a novel SGLT2 inhibitor, is known to improve glycemic levels by increasing the urinary excretion of glucose by the kidneys.^{23,24} SGLT2 are transporter molecules that facilitates the reabsorption of 90% of the filtered glucose in the early proximal tubule. Hence, the inhibition of SGLT2 significantly reduces the reabsorption of filtered glucose, resulting in the excess excretion of glucose in the urine.¹⁴ Empagliflozin has shown to provide dose-dependent urinary glucose excretion of up to 90 g per day.¹⁴ Another benefit of the drug is low hypoglycaemia risk due to the insulin-independent mechanism of action of the drug.^{23,24}

The present study demonstrated that add-on empagliflozin therapy can significantly decrease fasting and postprandial blood glucose levels in T2DM patients with inadequate response to triple drug therapy. A significant improvement in HbA1c% was noted within 3 months of treatment and a remarkable proportion of the subjects (46.34%) achieved HbA1c levels $<0.7\%$. Also, the fasting and postprandial blood glucose levels were noted to be significantly different during the first, second and third month of treatment, when compared to the pre-treatment

values. Robust evidence substantiates the glycemic efficacy and safety of empagliflozin.²⁴ A meta-analysis of randomized controlled trials by Devi et al. (2017) have concluded on the efficacy and safety of empagliflozin as monotherapy and add-on to existing diabetes pharmacotherapy for the treatment of T2DM.²¹ The study showed that the drug significantly improved HbA1c levels and fasting plasma glucose levels when used as an add-on to existing drugs. The drug also exhibited potential reduction in HbA1c% even in T2DM patients with 2nd or 3rd stage of chronic kidney diseases.¹³

Studies have demonstrated that empagliflozin treatment, as monotherapy or as add-on, confers several non-glycemic effects such as reduction in blood pressure and body weight.²¹ The present study findings are in line with these inferences. A significant reduction was noted in the body weight of 27 subjects following the treatment. Empagliflozin contributes to weight reduction through the loss of 240 to 400 Kcal/day into the urine.²³ Certain studies have suggested that the drug may increase the risk of hypoglycaemia, genital and urinary tract infection, when used either as monotherapy or as add-on therapy.²¹ Whereas, the present study did not report any severe adverse effects, except mild hypoglycaemia, UTI and mycotic infection.

Literature review shows immense evidence on the long-term and short-term safety and tolerability of empagliflozin for T2DM management.²⁵ Shiba et al. (2017) have studied the safety of empagliflozin among Japanese diabetic patients and reported the drug as well-tolerated, with no case of hypoglycaemia requiring assistance.²⁶ Kohler et al. (2016), evaluating the safety and tolerability of empagliflozin, in >9000 pooled data of patients from 14 clinical trials, reported 10 mg and 25 mg doses of empagliflozin as well tolerated in T2DM patients.²⁷ The study noted only 0.2% and 0.3% incidence of UTI, in patients on 10 mg and 25 mg of empagliflozin, compared to 0.4% incidence noted in the placebo group. However, the incidence of genital infection was 4.7% and 5% respectively in the patients receiving 10 mg and 25 mg of empagliflozin, compared to only 1.3% in the placebo group. A higher risk of hypoglycaemia was noted in patients on background insulin and/or sulfonylurea. There was no associated higher risk of hypoglycaemia in T2DM patients receiving empagliflozin, compared to the placebo group. The incidence of malignancies, fractures, hepatic injury, venous thromboembolic events, impairment in renal function and diabetic ketoacidosis were similar across the treatment groups.²⁷

Several researchers have studied the effect of empagliflozin as an add-on to other oral anti-diabetic agents.^{7,28} Eirik et al. (2016) have evaluated the safety and efficacy of empagliflozin as an add-on to linagliptin and metformin in T2DM patients with inadequate disease control. The study reported that empagliflozin as a well-tolerated drug with improved glycemic control and weight loss compared to placebo, during a 24-week treatment period.²⁸ Empagliflozin has also been recommended for the treatment of T2DM in combination with insulin, with or

without other antidiabetic drug.²⁹ Investigations on addition of empagliflozin to basal-insulin have revealed that empagliflozin significantly decreases HbA1c, body weight and insulin sparing in 78-week time duration, compared to the placebo.³⁰

This study could be considered as one of its kind, since a review of published literature did not show any study on the use of add-on empagliflozin to existing triple drug treatment involving glimepiride, metformin and teneligliptin. This combination could be possibly a good choice in patients reluctant to receiving injectables like insulin. Injectables such as GLP-1 analogs, amylin analog or insulin is generally prescribed to T2DM patients showing inadequate response to triple drug treatment.^{31,32} In a prospective self-report survey involving 100 T2DM patients, Larkin et al. have reported that 33% of the T2DM patients were unwilling to take insulin injections.³³ The major concerns among the patients were less flexibility, permanent need of the therapy, organ damage, weight gain and the fear of hypoglycemia.³³⁻³⁵

The present study holds immense relevance, as the add-on treatment with empagliflozin may serve as an effective alternative to injectables for T2DM management. However, the study has certain limitations like small sample size, follow-up conducted for 3-months, single center evaluation and non-randomized study design. The study warrants the need for larger investigations of prospective cohort studies exploring the long-term efficacy and safety of the drug on disparate population to corroborate the present study findings.

CONCLUSION

In conclusion, empagliflozin may serve as an effective add-on in T2DM patients showing inadequate control to triple drug treatment of metformin, glimepiride and teneligliptin. The drug is well tolerated and can yield remarkable glycemic control in shorter duration.

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