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Research Paper

Safety and efficacy of addition of Empagliflozin in Patients of Type 2 Diabetes Mellitus who were Inadequately Controlled with basal insulin alone or its combination with other OHAs

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Abstract:
Objective: *To compare the efficacy and safety of empagliflozin in treatment of patients with type 2 diabetes mellitus inadequately controlled with insulin alone or its combination with other OHAs.*
Materials and methods: *This was an observational retrospective study conducted in 205 diabetic patients. A predesigned study pro forma were used to retrieve the clinical data from electronically stored* patients *profile at Diabetic OPD and patients admitted at Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar, India.*
Results:*85 patients were in group A and 120 patients were in group B.Significant weight and BMI reduction were observed in group A (-3.1 ± 2.4, p=0.001; -1.7 ± 0.7, p=0.001 respectively) and Group B (-2.7 ± 1.8, p=0.001; -1.9 ± 0.9, p=0.001 respectively). Almost similar HbA1c reduction observed in both the groups (p=0.001). Group B has higher reduction in insulin dose (-12.1 ± 6.1, p=0.001) as compare to group A (-11.4 ± 5.8, p=0.001). UTI and hypoglycemic events were minimal in both the groups. Despite there were a hypoglycemic events observed in both the group but none required any medical assistance.*
Conclusion: *In this study addition of empagliflozin to insulin mono-therapy or combination of insulin + other OHAs, produced significant improvement in glycemic control. Empagliflozin was well tolerated, with significant weight loss and lower risk of hypoglycemia.*
Keywords:*Sodium glucose co- transporter 2 Inhibitor, empagliflozin, insulin, type 2 diabetes.*

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I. INTRODUCTION:

Prevalence of diabetes mellitus has increased disproportionately and over the last few decades worldwide it became the leading health concern and by 2045 it is estimated to be 629 million [1,2]. Lifestyle modification can further prevent or delay the progression of type 2 diabetes [3,4], but in most of the cases pharmacotherapy with oral hypoglycemic agents (OHAs) or insulin or even their combinations for management of the glycemic status of the patient is an integral and indispensable modality [5].

In type 2 diabetes patients for the management of hyperglycemia, injectable therapy like insulin is a preferred option and even widely used as first line therapy as this therapy has documented benefits like reduction in microvascular complication and preserve the β-cell function [6,7]. Although in developing countries use of insulin has its own limitations like increasing number of hypoglycemic events and lack of compliance due to needle fear [8].

Use of various hypoglycaemic agents along with individualized approach for management of the optimal HbA1c target has been proposed by various international guidelines as it is relatively difficult to achieve optimal management of T2DM [9]. Hence a combination therapy of either different OHAs or with insulin is required in the treatment of T2DM and usually achieved through patients' acceptance to the therapy.

After the emergence of SGLT2i and DPP4i, more favorable studies sports its uses to achieve target blood glucose level even in uncontrolled T2DM patients who were not accepting insulin because of injection related non-compliance specially due to fear of daily insulin injections [10-13]. SGLT2 inhibitors as confirmed in various landmark randomised trials, have beneficial renal and cardiovascular effects in addition to their glucose-lowering effect in type 2 diabetic patients [14-17]. SGLT2i as an add on to metformin or other OHAs like DPP4i or SU or TZDs, do improve the glycemic status in T2DM patients as confirmed in various studies [18-20].

Among sodium-glucose co-transporter 2 (SGLT2), empagliflozin is one of the most potent one [18]. Because this action is independent of insulin, even after insulin secretion has waned significantly, SGLT2 inhibitors like empagliflozin may be used at any stage of type 2 diabetes.

Primary objective of this study is to compare the efficacy and safety of empagliflozin 10 mg in treatment of patients with type 2 diabetes mellitus inadequately controlled with insulin alone or its combination with other OHAs.

II. MATERIALS AND METHODS:

Study methods and population: This was an observational retrospective study conducted in 205 diabetic patients. A predesigned study pro forma were used to retrieve the clinical data from electronically stored patients profile from Diabetic OPDand patients admitted at Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar, India.

Patient eligibility

Inclusion criteria: Patients who were aged > 18 years, inadequately controlled (HbA1c > 7%) with insulin alone or in combination with other OHAs and having clinical records of at least 6 months were included in this observational retrospective study.

Exclusion criteria: Patients who were having any degree of macro and micro vascular complications, treatment with anti-obesity drugs 3 months prior to consent, history of type 1 diabetes mellitus, pregnant and lactating females were excluded from the study.

Study measurements: The primary endpoint of the current study was the change in glycemic profile including HbA1c from baseline to week 24 with empagliflozin 10 mg. Secondary endpoints of the current study include changes in fasting plasma glucose (FPG), post prandial plasma glucose (PPG), weight, BMI and daily insulin dose from baseline. Safety assessment were measured with confirmed hypoglycemia event (plasma glucose ≤70 mg/dl and/or requiring assistance) and incidence of urinary tract infection (UTI).

Statistical analysis: SPSS software were used to analyse the clinical data. Descriptive statistics were used to analyse statistical variables (i.e. frequencies were used for categorical variables and mean, standard deviation was used for continuous variables). A *P* value of less than 0.05 was considered statistically significant.

III. RESULTS:

Total 205 patients were included in this retrospective observational study, in which 85 patients were in group A and 120 patients were in group B. Demographic details of both the group were listed in table 1. Group B has longer duration of diabetes as compare to group A. Both the group has received > 40 units daily dose of insulin at baseline.

Table 1: Principal clinical parameters for study participants at baseline

Parameters	**Group A (N=85)**	**Group B (N=120)**	**P Value**
Male (*n* [%])	48 (56%	74 (62%)	0.326
Age (Years)	47.9 ± 14.4	44.6 ± 14.7	
Weight (Kg)	67.4 ± 10.8	65.6 ± 14.1	0.517
BMI (kg/m2)	26.2 ± 3.4	25.5 ± 5.4	0.371
Disease duration (year)	5.6 ± 1.3	10.3 ± 6.8	0.532
HbA1c level (%)	8.3 ± 0.6	8.1 ± 0.7	0.717
FPG (mg/dL)	189.7 ± 10.2	174.2 ± 11.6	0.231
PPG (mg/dl)	296.3 ± 21.4	284.8 ± 20.2	0.331
SBP (mmHg)	131.7 ± 15.6	129.83± 16.8	0.248

DBP (mmHg)	79.5 ± 3.7	78.5 ± 2.9	0.869
T-chol (mg/dL)	208.3 ± 34.6	202.8 ± 23.6	0.683
LDL-C (mg/dL)	111.2 ± 26.1	109.3 ± 21.4	0.538
HDL-C (mg/dL)	53.5 ±3.2	54.7 ±2.8	0.573
TG (mg/dL)	131.4 ± 57.8	128.5 ± 51.5	0.616
Insulin dose (IU/d)	43.2 ± 29.8	41.5 ± 25.7	0.968

In group B various other oral OHAs were used along with basal insulin. Concomitant antidiabetic drugs used in group B were listed in table 2. Apart of metformin (93%), DPP4i (51%) and sulfonylurea (48%) were the commonest oral OHAs used followed by thiazolidinedione (18%) and α-GI (16%).

Table 2: Concomitant oral OHAs drug (*n* [%]) used in group B

Drugs	**N (%)**
Metformin	112 (93%)
Sulfonylurea	58 (48%)
α-GI	19 (16%)
Thiazolidinedione	21 (18%)
DPP4i	61 (51%)

Change in clinical parameters for study participants from baseline to 24 weeks were listed in table 3. Significant weight and BMI reduction were observed in group A (-3.1 ± 2.4, p=0.001; -1.7 ± 0.7, p=0.001 respectively) and Group B (-2.7 ± 1.8, p=0.001; -1.9 ± 0.9, p=0.001 respectively). Almost similar HbA1c reduction observed in both the groups (p=0.001). Group B has higher reduction in insulin dose (-12.1 ± 6.1, p=0.001) as compare to group A (-11.4 ± 5.8, p=0.001).

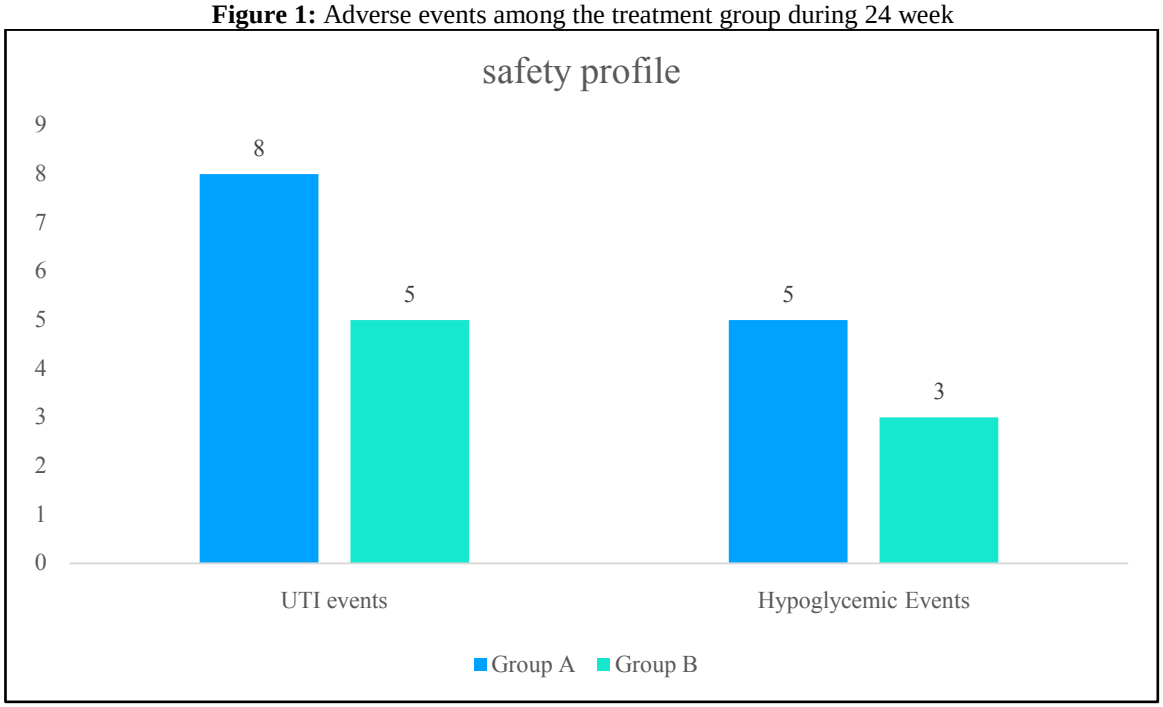
Table 3: Change in clinical parameters for study participants from baseline to 24 weeks

Group	**Group A**				**Group B**			
	Baseline	**24 week**	**Mean Difference**	**P Value**	**Baseline**	**24 week**	**Mean Difference**	**P Value**
Weight (Kg)	67.4 ± 10.8	64.3± 15.5	-3.1 ± 2.4	0.001	65.6 ± 14.1	63.1± 14.7	-2.7 ± 1.8	0.001
BMI (kg/m2)	26.2 ± 3.4	24.5 ± 6.5	-1.7 ± 0.7	0.001	25.5 ± 5.4	23.6± 7.1	-1.9 ± 0.9	0.001
HbA1c (%)	8.3 ± 0.6	7.2 ± 0.5	-1.1 ± 0.6	0.001	8.1 ± 0.7	7.1 ± 0.5	-1 ± 0.4	0.001
FPG (mg/dl)	189.7 ± 10.2	126.5 ± 8.7	-63.2 ± 21.4	0.001	174.2 ± 11.6	120.6 ± 6.5	-53.6 ± 23.5	0.001
PPG (mg/dl)	296.3 ± 21.4	189.7 ± 16.9	-106.6 ± 34.3	0.001	284.8 ± 20.2	172.1 ± 12.7	-112.7 ± 42.6	0.001
Insulin dose (IU/d)	43.2 ± 29.8	31.8 ± 16.3	-11.4 ± 5.8	0.001	41.5 ± 25.7	29.4 ± 15.5	-12.1 ± 6.1	0.001

Figure 1 demonstrated the safety profile of empagliflozin when added to both the groups. UTI and hypoglycemic events were minimal in both the groups. Despite there were a hypoglycemic events observed in

both the group but none required any medical assistance. The hypoglycemic events were measured by individual glucometers.

Figure 1: Adverse events among the treatment group during 24 week



IV. DISCUSSION:

In the modern management of type 2 diabetes mellitus SGLt2i have emerged as important targets and its use are increasing as an alternative or additional oral hypoglycemic drug.

There are plethora of trials which confirms the superior efficacy of empagliflozin in glycemic control [21,22]. In a recent study in addition to standard care those who received empagliflozin had lower rates of death from any cause and rates of the primary composite cardiovascular outcome among patients with type 2 diabetes who were at high risk for cardiovascular events [23, 24]. In current study there were a statistically significant reduction of FPG observed in both Group A and Group B (-63.2 ± 21.4, p=0.001; -53.6 ± 23.5, p=0.001, respectively) and as well as PPG (-106.6 ± 34.3, p=0.001; -112.7 ± 42.6, p=0.001, respectively). In line with our observation similar results regarding glycemic efficacy was also reported by Gupta S et al [25] and Puli. K et al [26] in same kind of Indian patient setting.

In obese patients daily insulin dose is one of the major concern. In a recent clinical trial empagliflozin has shown a significant reduction in daily insulin requirement as compared to placebo in addition with potent glycemic control [27] and even data on Indian patients established the same [28,29]. In line with the mentioned trials, even in current study there were a significant reduction of insulin dose in both group A and B (-11.4 ± 5.8, p=0.001; -12.1 ± 6.1, p=0.001 respectively).

Among nonglycemic benefits, empagliflozin offers significant weight reduction. Our results also show that additional treatment with empagliflozin led to a significant decrease in body weight in both the group. This finding is essential as with major antidiabetic drugs weight gain being a common side effect and in most patients maintaining clinically meaningful weight is a challenge [30, 31]. It was well established that insulin treatment resulted in weight gain [32-34] and that can further deteriorate when insulin is added with sulfonylurea [35,36]. It has been generally assumed that treatment with SGLT2i like empagliflozin does not affect body weight, whereas treatment associated with empagliflozin leads to a reduction in body weight [37,38].

In line with the earlier studies, hypoglycemia and chance of UTI were likely to be minimal with empagliflozin. No severe hypoglycemia were encountered in both the groups and required no rescue therapy or addition medical assistance.

Limitation

Short duration, absence of control group and small sample size were the major limitations of this trial. Studies of longer duration to measure parameters other than glycemic control are required.

V. CONCLUSION:

In this study addition of empagliflozin 10 mg to insulin mono-therapy or combination of insulin + other OHAs, produced significant improvement in glycemic control. Empagliflozin was well tolerated, with significant weight loss and lower risk of hypoglycemia. Addition of empagliflozin to both group treatment modalities were generally well tolerated in this study. Costs in healthcare significantly improved in recent days for diabetic patients mainly because of increasing obesity and hypoglycemic events and therefore increased complications and decreased quality of life. Observation of the current clinical study established need of hypoglycemic agents like empagliflozin with additional benefits.

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