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A STUDY ON EFFICACY AND SAFETY OF DAPAGLIFLOZIN AMONG PATIENTS ATTENDING A TERTIARY CARE CENTER IN BIHAR

Pharmacology

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ABSTRACT

Type 2 diabetes mellitus (T2DM) has reached epidemic proportions affecting 56 million people in Europe, accounting for 8.5% of the adult population. Prevalence of T2DM is expected to increase in the following years with projections suggesting that 69 million Europeans will be affected by 2035 (10.3% of the adult population). **MATERIALS AND METHODS:** This retrospective observational study was planned and executed by Department of Pharmacology, Government Medical College & Hospital, Bettiah, Bihar. The purpose of the study was to investigate the effectiveness and renal safety of dapagliflozin 10 mg once daily in adults with type 2 diabetes mellitus who were also receiving metformin 1.5–2.5 g/day (DAPA + MET). Prior ethical clearance was obtained from the Institutional Ethics Committee. **RESULTS:** Out of 68 patients recruited on the data, complete data could be obtained for 62 patients. Thus, the final analysis was done on 62 patients. Baseline data and demographic details has been given on table. **CONCLUSION:** Glycemic control was more likely to be achieved in patients treated with dapagliflozin alone or in combination with metformin, while add-on therapy with insulin and/or glimepiride was not associated with further improvement in HbA1c levels.

KEYWORDS

Type 2 diabetes mellitus, Dapagliflozin

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has reached epidemic proportions affecting 56 million people in Europe, accounting for 8.5% of the adult population. Prevalence of T2DM is expected to increase in the following years with projections suggesting that 69 million Europeans will be affected by 2035 (10.3% of the adult population) [1]. The pathophysiology of T2DM is characterized by insulin resistance and progressive loss of β-cell function. Treatment is based on the use of therapeutic agents that address these problems. Nevertheless, available therapeutic options have also significant limitations, such as increased risk of hypoglycemia with sulphonylureas and insulin. Moreover, management of comorbidities including obesity and hypertension poses unique challenges.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a novel class of antihyperglycemic agents with an insulin-independent mode of action. Glucose filtered in the glomerulus is primarily reabsorbed in the S1 segment of the proximal convoluted tubule through the SGLT2. Pharmacologic inhibition of the SGLT2 results in glucosuria, thus lowering blood glucose levels. Dapagliflozin is a member of the SGLT2 inhibitors class that has received marketing authorization in Europe and the US. Dapagliflozin is indicated along with diet and exercise as monotherapy for patients with T2DM who are intolerant to metformin or for whom metformin is contraindicated. It can also be used as an adjunct to other glucose-lowering agents including insulin for patients with inadequate glycaemic control. In the US, the recommended starting dose for dapagliflozin is 5 mg once daily taken in the morning, which can be increased to 10 mg for patients requiring additional glycemic control [2]. Nevertheless, the approved summary of product characteristics in Europe suggests that dapagliflozin is initiated at a daily dose of 10 mg [3]. A fixed-dose combination of twice daily dapagliflozin 5 mg with metformin 850 or 1000 mg is also commercially available in Europe [4]. A similar, once daily, extended-release formulation of dapagliflozin with metformin was recently approved in the US.

The aim of this study was to evaluate the efficacy and safety of dapagliflozin in patients with type 2 diabetes among patients attending a tertiary care centre in India.

MATERIALS AND METHODS

This retrospective observational study was planned and executed by Department of Pharmacology, Government Medical College & Hospital, Bettiah, Bihar. The purpose of the study was to investigate the effectiveness and renal safety of dapagliflozin 10 mg once daily in adults with type 2 diabetes mellitus who were also receiving metformin 1.5–2.5 g/day (DAPA + MET). Prior ethical clearance was obtained from the Institutional Ethics Committee. Patients coming to the Out Patients Department of Medicine of the college for follow-up and have been of treatment with dapagliflozin for at least 12 months were included in the study. Other inclusion criteria were continuous therapy with no interruption in the course, normal renal function before the initiation of treatment, modified dietary habits and those who gave consent to participate in the study. Based on these criteria, 68 patients were recruited for the study.

Baseline characteristics included age, sex, weight and height for BMI, systolic blood pressure, diastolic blood pressure, and disease duration.Effectiveness was assessed using the change from baseline in HbA_{1c} at 6 and 12 months as well as changes in body mass index (BMI) and lipid parameters (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides) at 12 months. HbA_{1c} was self-monitored, with outpatient visits performed every three months or when needed. Renal function was assessed by the change in blood creatinine levels at 6 and 12 months, as well as urine microalbumin levels at 12 months.

Statistical analyses were performed using SPSS Statistics version 20. All variables were analyzed by summary statistical methods and the analyses were performed separately in patients who received DAPA + MET (group A) and DAPA + MET + other glucose-lowering drugs (group B). For continuous/quantitative variables, descriptive statistics, including the number of available values, arithmetic mean, standard deviation (SD), minimum, median, and maximum were calculated, while for categorical/qualitative variables, frequency tables were generated.

RESULTS

Out of 68 patients recruited on the data, complete data could be obtained for 62 patients. Thus, the final analysis was done on 62 patients.Baseline data and demographic details has been given on table 1. Concomitant therapies included angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers for hypertension, and statins for management of dyslipidemia. The baseline demographics and characteristics were not significantly different between group A and group B patients, with the exception of disease duration (Table 1).

When added to metformin, dapagliflozin significantly reduced HbA_{1c} levels from baseline in patients of both the groups (Figure 1). After 6 months of treatment, HbA_{1c} levels decreased by 0.5% and 0.9% in both the groups, respectively.This reduction was statistically significant ($p < 0.05$). After 12 months of treatment, HbA_{1c} levels decreased by 1.1% and 1.2% respectively. In group Bpatients, the change from baseline in

HbA_{1c} levels at 6 months was significantly greater than that in group B patients,however, no significant between-group difference was observed at 12 months. Over the 12-month treatment period, dapagliflozin significantly reduced BMI in all the patients. The change in BMI was by 0.8kg/m^2 and by 0.9kg/m^2 in group A and B, respectively. (Table 2), with no significant difference between two groups. No significant changes in lipid parameters over the study period were observed.

No detrimental effects on renal function were observed during the study. There were no significant changes from baseline in creatinine levels at 6 and 12 months in all patients (Figure 2). On the other hand, after 12 months, a significant reduction in microalbumin was observed in group A patients. (Table 2). The eGFR values in all patients remained above 60 mL/min throughout the study. No statistically significant variation in eGFR was observed between treatment groups.

Table 1: Baseline Laboratory Data And Demographic Details Of Patients Of Both The Groups

Characteristics	Group A (n = 32)	Group B (n = 30)
Age (years)	52 ± 7.2	54 ± 6.9
Female, (%)	41.8	39.6
BMI (kg/m^2)	31.3 ± 6.3	33.1 ± 5.4
Duration of disease (years)	7.9 ± 1.9	8.3 ± 4.8
Systolic BP (mm of Hg)	134.7 ± 16.9	136.8 ± 21.2
Diastolic BP (mm of Hg)	83.4 ± 3.5	81.8 ± 4.7
HbA1C	8.1 ± 3.2	9.3 ± 2.7
Creatinine (µmol/L)	74.9 ± 15.7	76.3 ± 15.4
Microalbumin (µg/mg)	118.8 ± 87.9	75.9 ± 48.9
eGFR (mL/min)	94.6 ± 26.8	95.4 ± 21.2
Total cholesterol (mg/dl)	182.6 ± 31.9	185.5 ± 43.6
LDL (mg/dl)	113.8 ± 31.1	108.1 ± 31.8
HDL (mg/dl)	47.8 ± 12.5	49.2 ± 12.6
Triglycerides (mg/dl)	142.6 ± 67.3	132.6 ± 55.8

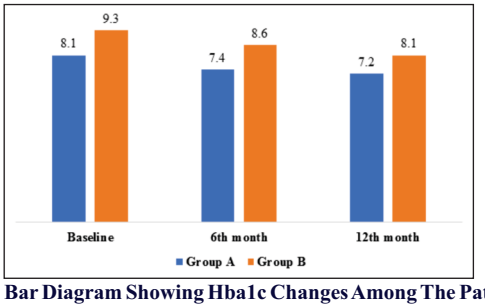

Fig. 1: Bar Diagram Showing Hba1c Changes Among The Patients Of Both The Groups Over The Course Of The Study

Table 2: Table Showing Data Of Characteristic Variable At 12th Month Duration With The Change In The Variable From The Baseline Data

Characteristics	Group A	Group B
BMI (kg/m^2)	30.1 ± 5.6	32.3 ± 4.8
Δ	-0.8	-0.9
Total cholesterol (mg/dl)	180.0 ± 28.9	174.2 ± 41.8
Δ	-2.6	-11.3
LDL (mg/dl)	109.6 ± 27.6	96.4 ± 22.5
Δ	-4.2	-11.7
HDL (mg/dl)	51.1 ± 9.4	50.5 ± 14.5
Δ	+ 3.3	+ 1.3
Triglycerides (mg/dl)	103.6 ± 64.7	128.4 ± 51.3
Δ	-3.9	-4.2
Microalbumin (µg/mg)	94.7 ± 82.6	79.7 ± 39.2
Δ	-24.1	-16.2

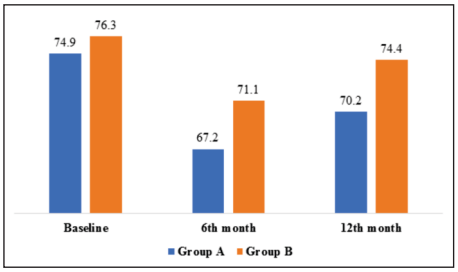

Fig. 2: Bar Diagram Showing Changes In Serum Creatinine Among The Patients Of Both The Groups Over The Course Of The Study

DISCUSSION

This retrospective observational study investigated the effectiveness and safety of add-on therapy with dapagliflozin in patients with type 2 diabetes treated at a single facility in a medical college hospital in Bihar. The results demonstrate that dapagliflozin is effective and safe. Dapagliflozin significantly reduced HbA_{1c} levels after 12 months of treatment regardless of whether other glucose-lowering agents were received. In both patients, significant reductions were apparent from 6 months. Contrary to expectations, greater reductions were obtained in patients who received DAPA + MET, that is, those who received no additional therapy. We did not find any negative effects on renal function (assessed by blood creatinine and urine microalbumin levels) during the study. Microalbumin reduction was observed in patients who received DAPA + MET alone but we cannot exclude, due the nature of our study, other potential factors that could explain this exclusive effect.

The results of this study are in line with those of other studies of dapagliflozin conducted in patients with type 2 diabetes inadequately controlled with metformin [5-13].

This study had a number of limitations due to its retrospective observational design. It used data from an unselected group of patients and the size of the patient population was not as large as in other studies conducted in patients with type 2 diabetes. Furthermore, no measures were taken to control for confounding factors. This, in combination with a lack of a control group, means that this study cannot adequately explain the finding that patients treated with DAPA + MET experienced greater reductions in HbA1c levels compared with those who received additional glucose-lowering drugs. The strengths of this study, on the other hand, included the length of the observational period and the fact that it was conducted in a real-life setting. These factors improve the generalizability ofits findings.

CONCLUSION:

This retrospective observational study demonstrates that dapagliflozin is effective in reducing HbA_{1c} levels and safe when administered in patients with type 2 diabetes also receiving metformin. Glycemic control was more likely to be achieved in patients treated with dapagliflozin alone or in combination with metformin, while add-on therapy with insulin and/or glimepiride was not associated with further improvement in HbA_{1c} levels.

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