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Original Article

Internal Medicine Section

A Prospective Observational Study to Compare the Efficacy and Adverse Effects of Glimepiride and Vildagliptin Added to Metformin in Type 2 Diabetes Mellitus

BISWANATH SHARMA SARKAR[1], SHUVANKAR MUKHERJEE[2], MANIKANTA MAJI[3], SUMAN BISWAS[4]

ABSTRACT

Introduction: In order to prevent the specific diabetes mellitus related macrovascular and microvascular complications, guidelines by American Diabetes Association recommend a reasonable glycosylated haemoglobin goal for non-pregnant adults to be less than 7% (53 mmol/mol). The common practice recently is to use a sulfonylurea like glimepiride or selective Dipeptidyl Peptidase-4 (DPP-4) inhibitor like vildagliptin as add-on therapy to metformin when the latter alone fails to achieve the target level of sugar control. Many randomised clinical trials have demonstrated the comparative efficacy of glimepiride and vildagliptin as add-on therapy to metformin. But their results might not always reflect what actually could be expected in clinical practice.

Aim: To compare the efficacy and safety of glimepiride and vildagliptin as add-on therapy to metformin in achieving glycaemic control and also to compare the common adverse effects observed.

Materials and Methods: This prospective observational study was conducted among adult type 2 diabetes mellitus patients who did not achieve adequate glycaemic control with metformin monotherapy. Patients were purposively selected in a way so that 30 patients received 2 mg of glimepiride once daily and 30 received 50 mg of vildagliptin twice daily as add-on therapy to metformin 1.5 to 2 gm in single or divided doses. Fasting, post-prandial sugar and glycosylated hemoglobin levels were re-examined after 4 to 6 months. Data were analysed using SPSS version 20.0. Paired and unpaired T-tests were applied to compare the parametric data and z-test was used to compare the difference between two proportions at 5% significance level.

Results: In both the groups there was a significant reduction in mean FBS, PPBS levels and HbA1c% from the baseline ($p<0.001$). The mean of reduction in FBS and PPBS levels did not vary significantly between the two groups ($p>0.05$). However, glimepiride plus metformin reduced mean HbA1c% significantly more than vildagliptin plus metformin ($p<0.001$). The glimepiride group caused significantly more hypoglycaemia than the vildagliptin group ($p=0.03$) while vildagliptin group was significantly more associated with overall gastrointestinal symptoms ($p=0.046$). There was no significant difference in weight gain between the two groups ($p=0.084$).

Conclusion: Glimepiride appeared to be superior to vildagliptin in reducing the HbA1c level but at the cost of significantly more episodes of hypoglycaemia than vildagliptin while latter added to metformin produced significantly more gastrointestinal side effects than the former.

Keywords: Dipeptidyl peptidase-4 inhibitor, Glycosylated haemoglobin, Metformin combination therapy, Sulfonylurea

INTRODUCTION

India has been under the clutches of the epidemic of type 2 diabetes mellitus, which accounts for more than 90% of all the diabetes mellitus cases and currently leads the world, as it has the highest number of diabetics and is considered as the "diabetes capital of the world" [1]. The International Diabetes Federation (IDF) has estimated the total number of diabetic subjects to be around 40.9 million in India, which will further rise to 69.9 million by the year 2025 [2]. The significant burden of type 2 diabetes mellitus is closely related to the specific diabetes-related macrovascular complications namely ischemic heart disease, stroke and peripheral vascular disease and resultant amputations, as well as microvascular changes leading to blindness, renal failure and peripheral neuropathy [3-5]. Guidelines by American Diabetes Association (ADA) recommend a reasonable glycosylated haemoglobin (HbA1c) goal for non-pregnant adults to be less than 7% (53 mmol/mol) in order to prevent these complications [6]. However, to achieve this many cases of type 2 diabetes mellitus require two or more Oral Hypoglycaemic Agents (OHA) to be used as combination therapy [7]. The common practice in recent days is to use a sulfonylurea like glimepiride or selective DPP-4 inhibitor like vildagliptin as add-on therapy to metformin when the latter alone fails to achieve the target level of sugar control [7-11]. Many Randomized Clinical Trials (RCTs) have demonstrated the comparative efficacy of glimepiride and vildagliptin as add-on therapy to metformin [12-15]. However, RCTs meeting scientific standards and regulations often produce results that might not always reflect what actually could be expected in day-to-day clinical practice. The resultant gap in information could be filled up by carrying observational trials [14,16,17].

In this backdrop the present study was conducted with the objective to compare the efficacy of glimepiride and vildagliptin as add-on therapy to metformin in achieving glycaemic control and also to compare the common adverse effects observed.

MATERIALS AND METHODS

This prospective observational study was conducted in the department of General Medicine at Bankura Sammilani Medical College, in Bankura district of West Bengal between December 2017 and June 2018. The study population comprised of patients having type 2 diabetes mellitus aged 18 years and above, who were not adequately controlled with metformin monotherapy up to the dose of 2 gm/day, as reflected by HbA1c level more than 7%, and were prescribed by the attending physicians either 2 mg of glimepiride once daily or 50 mg of vildagliptin twice daily along with metformin 1.5 to 2 gm in single or divided doses as add-on therapy to metformin. Patients having history of diabetic ketoacidosis, acute myocardial infarction or

unstable angina, cerebrovascular accidents in the past six months and patients having diabetic nephropathy (with serum creatinine ≥1.5 mg/dL) and/or grossly deranged liver function tests (with total serum bilirubin ≥2 mg/dL, serum SGPT and SGOT >3 times the upper limit of normal) were excluded from the study. The study got clearance from the ethics committee of the institution (registration no: EC/BSMCH/Aca/113/2017) and informed consent was obtained from each patient before they were included in the study. In the first month of the study period considering feasibility of follow-up it was decided purposively that an arbitrary number of 60 patients would constitute the final sample size. Allocation of treatment regimen was done by the treating physicians according to their clinical judgment only and no randomisation was attempted. Finally, following the inclusion and exclusion criteria, patients were selected consecutively until 30 patients receiving glimepiride plus metformin and 30 receiving vildagliptin plus metformin in the aforementioned doses and schedule, could be included in the study.A pre-designed and pre-tested patient record form was used to record the socio-demographic variables, findings of physical examination and biochemical test reports. Baseline measurement of Fasting and Postprandial Blood Sugar (FBS and PPBS), HbA1c%, complete hemogram, serum total cholesterol, urea and creatinine were done for all the study subjects in the Department of Biochemistry of the study institution. Height and weight were measured and Body Mass Index (BMI) was calculated accordingly. Weight was measured at each visit. The patients were provided with the prescribed medicines from the hospital pharmacy for one month and were advised to attend the out-patient department each month. For the most part patients were contacted over mobile phone and were reminded about the follow-up date. Fasting and post-prandial sugar and HbA1c% were re-examined after four months with a relaxation period of up to six months as some patients could not come for review on the 4th month of the follow-up period. Adverse events like hypoglycaemia, overall gastrointestinal symptoms like nausea, vomiting, diarrhea, flatulence, abdominal pain were noted along with weight gain. Minor dose adjustments were made in a few patients in both the treatment groups in case of complains of hypoglycaemia and gastric intolerance. After consultation with treating physician, most of them soon reverted back to the original dose after adjusting the frequency of meals, timing of the medicines intake and use of PPI for a short period. However all of these cases were included in the final analysis. Each patient was advised to follow appropriate dietary and exercise regimens.

STATISTICAL ANALYSIS

Data were analysed using SPSS (Statistical Package for Social Scientists) version 20.0, IBM, Armonk, New York, USA. Paired and unpaired t-tests were applied to compare the parametric data and z-test was used to compare the difference between two proportions. A p-value of less than equal to 0.05 was considered statistically significant.

RESULTS

The glimepride-metformin group consisted of 30 patients with an age range between 31 to 87 years, while the vildagliptin-metformin group comprised of 30 patients aged between 25 to 73 years. It was found that the age and sex composition of the two groups did not vary significantly (p>0.05). Also, the baseline parameters like BMI, serum urea, creatinine, total cholesterol, FBS, PPBS and HbA1c% did not vary significantly among the two groups (p>0.05) [Table/Fig-1]. In both the groups there was a significant reduction in mean FBS, PPBS levels and HbA1c% from the baseline (p <0.001) [Table/Fig-2]. The mean of reduction in FBS (53.2±21.9 vs. 46.5±26.9 mg/dL) and PPBS (84.3±55.3 vs. 82.5±12.7) levels did not vary significantly between the two groups (p>0.05). However, glimepiride added to metformin reduced mean HbA1c% significantly more than that by adding vildagliptin to metformin (1.4±0.08 vs. 1.0±0.09) (p<0.001) [Table/Fig-3].

It was also observed that the glimepiride group caused significantly more hypoglycaemia than the vildagliptin group (p=0.03) while vildagliptin group was significantly more associated with overall gastrointestinal symptoms than the glimepiride group (p=0.046). There was no significant difference in weight gain between the two groups (p=0.084) [Table/Fig-4].

Characteristic	Metformin+Glimepiride (n=30)	Metformin+Vildagliptin (n=30)	p-value
Age (years)	52.4±12.0	50.90±10.6	0.62
Sex			
Male	10 (43.5%)	13 (56.5%)	0.43
Female	20 (54.1%)	17 (45.9%)	
BMI (kg/m^2)	26.2±7.8	24.6±6.9	0.40
Urea (mg/dL)	33.4±7.0	32.3±6.6	0.56
Creatinine (mg/dL)	0.9±0.2	1.0±0.2	0.29
Total cholesterol (mg/dL)	161.2±31.4	155.4±19.9	0.40
FBS (mg/dL)	175.6±47.1	161.8±50.3	0.28
PPBS (mg/dL)	277.3±68.3	256.2±78.4	0.27
HbA1C (mmol/mol)	67.2±12.3	62.8±10.3	0.14
HbA1C%	8.3±1.1	7.9±1.0	0.14

[Table/Fig-1]: Patient characteristics in the two treatment groups.

Group	Biochemical parameters	Mean	SD	p-value
Metformin+Glimepiride	FBS1 (mg/dL)	175.6	47.1	<0.001*
	FBS2 (mg/dL)	122.4	31.9	
	PPBS1 (mg/dL)	277.3	68.3	<0.001*
	PPBS2 (mg/dL)	193.0	70.7	
	HBAIC1 (%)	8.3	1.1	<0.001*
	HBA1C2 (%)	6.9	1.1	
Metformin+Vildagliptin	FBS1 (mg/dL)	161.8	50.3	<0.001*
	FBS2 (mg/dL)	115.2	28.9	
	PPBS1 (mg/dL)	256.2	78.4	<0.001*
	PPBS2 (mg/dL)	173.6	74.9	
	HBAIC1 (%)	7.9	0.9	<0.001*
	HBA1C2 (%)	6.9	0.9	

[Table/Fig-2]: Achievement of glycaemic control in each treatment group before and after intervention.
FBS1=Baseline FBS level FBS2=FBS level checked between 4 to 6 months PPBS1=Baseline PPBS level PPBS2=PPBS level checked between 4 to 6 months HBAIC1 (%)=Baseline HBA1C% HBA1C2 (%)=HBA1C% checked between 4 to 6 months *Paired t-test was applied

Biochemical parameters	Metformin+Glimepiride (n=30)	Metformin+Vildagliptin (n=30)	p-value
	Mean±SD	Mean±SD	
FBS	53.2±21.9	46.5±26.9	0.30
PPBS	84.3±55.3	82.5±12.7	0.87
HbA1C%	1.4±0.08	1.0±0.09	<0.001*

[Table/Fig-3]: Comparison of anti-hyperglycaemic effect of the two treatment groups.
*Unpaired t-test was applied

Adverse events	Metformin+Glimepiride (n=30)	Metformin+Vildagliptin (n=30)	p-value
Hypoglycaemia	8 (26.7)	1 (3.3)	0.03*
Gastrointestinal symptoms	2 (6.7)	9 (30.0)	0.046*
Weight gain	8 (26.7)	2 (6.7)	0.084

[Table/Fig-4]: Comparison of adverse events between the two groups.
Figures in parentheses indicate percentage
* z-test to compare two rates was applied

DISCUSSION

The present study aimed at comparing the efficacy of glimepiride and vildagliptin as add-on therapy to metformin in achieving glycaemic control and also to compare the common adverse effects observed

under clinical setting outside the influence of RCT. It was observed that in both the treatment groups the mean FBS, PPBS and HbA1c% decreased significantly from the baseline. Both the treatment regimens are similar in reducing FBS and PPBS. However, glimepiride added to metformin showed significantly more reduction in HbA1C than vildagliptin and metformin. Gullapalli and Desai in a non-randomized longitudinal intervention study from Karnataka found that in both glimepiride and vildagliptin groups the mean FBS, PPBS and HbA1c% decreased significantly from the baseline at the end of 12 weeks [18]. The same study also showed that the decrement in mean FBS was significantly more in the vildagliptin group than in the glimepiride group. However, there was no significant difference in the reduction in the mean PPBS and HbA1c% between the two groups [18]. Jeon HJ et al., in a randomized open-label comparative study in Korea found no significant difference in reduction in the mean FBS, PPBS and HbA1c% between glimepiride-metformin and vildagliptin-metformin groups [7]. Filozof C et al., from their RCT revealed that in patients inadequately controlled with metformin, vildagliptin add-on provided similar HbA1c-lowering efficacy compared with another sulfonylurea, gliclazide, after 52 weeks of treatment [19]. After comparing results from RCTs with observational trials Ahrén B et al., reported that the reduction in HbA1c with sulfonylurea treatment was actually lower in real life relative to RCTs, while on the other hand for vildagliptin, the improvement in glycaemic control was the same in RCTs as well as in observational trials [14]. The authors attributed this to the fear of hypoglycaemia and the associated weight gain with the use of sulfonylureas in real life situation [14]. In fact in the present study it was observed that the glimepiride group caused significantly more hypoglycaemia than the vildagliptin group which was similar to findings of other studies [13,15,18]. However, in the present study there was no significant difference in weight gain between the two groups. Moreover, the overall occurrence of gastrointestinal symptoms in the present study was significantly higher in the vildagliptin group than in the glimepiride group, a finding similar to that reported by Jeon HJ et al., [7]. Although combination treatment with vildagliptin-metformin might have a greater potential to induce gastrointestinal side effects compared to glimepiride-metformin [7], studies conducted earlier did not show any further increase in gastrointestinal side effects between metformin monotherapy and metformin-vildagliptin combination therapy [20,21].

LIMITATION

The present study had its own limitations. First of all, arbitrary selection of sample size might not have been adequate and non-randomisation into the groups might have involved some selection bias. Secondly, adherence to medications, diet and exercise were self reported and thus could have led to subjective bias. However, the present study revealed a fair amount of knowledge regarding the comparative efficacy of the two treatment groups in clinical practice situation.

CONCLUSION

It could be concluded from the present study that although as add-on therapy to metformin both glimepiride and vildagliptin could significantly achieve the target glycemic control, glimepiride-metformin in comparison to vildagliptin-metformin showed a significantly more reduction in HbA1c%. But this was achieved at a significantly higher risk of hypoglycemia with the former regimen. On the other hand vildagliptin-metformin produced significantly more gastrointestinal side effects than the glimepiride-metformin therapy. The present researchers would like to recommend that, owing to the lower risk of hypoglycaemia, vildagliptin add-on to metformin could be a better alternative to glimepiride add-on to metformin in elderly groups who could be more susceptible to hypoglycaemia.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of General Medicine, Bankura Sammilani Medical College, Bankura, West Bengal, India.
2. Assistant Professor, Department of Community Medicine, Calcutta National Medical College, Kolkata, West Bengal, India.
3. Senior Resident, Department of General Medicine, Barjora Super Speciality Hospital, Bankura, West Bengal, India.
4. Independent Researcher, Department of Community Medicine, Calcutta National Medical College, Kolkata, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Shuvankar Mukherjee,
18, East Road, Jadavpur, Kolkata-700032, West Bengal, India.
E-mail: mukherjeesm2012@gmail.com

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