Original Research Article

Comparative study of change of HbA1c with voglibose and teneligliptin on ongoing metformin monotherapy

Pratyay Pratim Datta[1*], Ratneshwar Bhattacharya[2], Sukanta Sen[3], Chandra Narayan Gupta[4]

[1]Block Medical Officer of Health, Kotshila Rural Hospital, Jaldah-II, Purulia, West Bengal 723213, India
[2]Associate Professor, Department of General Medicine, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal 721645, India
[3]Professor & Head, Department of Pharmacology, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal 721645, India
[4]Associate Professor, Department of General Medicine, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal 721645, India

Received: 28-06-2020 / Revised: 30-07-2020 / Accepted: 03-08-2020

Abstract

Background: Metformin is a biguanide used as first line treatment of type 2 diabetes mellitus. When Metformin alone is unable to control glycaemic status properly then additional drug needs to be added. Some of the additional drugs reduce primarily fasting blood sugar (FBS) and some reduce post prandial blood sugar (PPBS). Voglibose and Teneligliptin are primarily capable of reducing PPBS. Overall hyperglycaemia is also controlled by these drugs. In this background the present study was planned for comparative study of Voglibose and Teneligliptin to reduce HbA1c ongoing Metformin monotherapy. **Materials & Methods**: It was a hospital based longitudinal interventional study among patients attending General Medicine Outpatient Department (OPD) of a Medical College, East Medinipur, West Bengal with uncontrolled hyperglycemia and whose HbA1c was above 7 but up to 10% and PPBS above 200mg/dl. One group of patients was given voglibose 0.3mg TDS and another group of patients were given teneligliptin 20mg BD in addition to previous dose of metformin. After 12 weeks of starting additional drug again HbA1c level was assessed for each patient. **Results:** It was found that mean HbA1c level at the beginning was 8.89% for voglibose group and 8.83% for teneligliptin group. There was no significant difference between these two. After 12 weeks of therapy the mean HbA1c level of voglibose group was significantly higher than teneligliptin group. However both groups showed significant reduction of HbA1c as compared to starting. **Conclusion:** The study highlights the ability to reduce HbA1c is more with teneligliptin 20mg BD than voglibose 0.3mg TDS.

Keywords: Type 2 Diabetes, glycosylated haemoglobin (HbA1c), fasting blood sugar (FBS), post prandial blood sugar (PPBS), metformin, voglibose, teneligliptin.

Introduction

Diabetes mellitus is now a days one of the most common non communicable disease in India. Approximately 8.8% adults aged 20-79 years are suffering from diabetes according to a study in 2017 [1]. Diabetes mellitus has different types of entity of which commonest form is Type 2 diabetes mellitus.

**Correspondence*
Dr. Pratyay Pratim Datta
Block Medical Officer of Health, Kotshila Rural Hospital, Jaldah-II, PO- Jindaru, Purulia, West Bengal 723213, India
E-mail: pratyaypratimdatta@gmail.com

Type 2 diabetes mellitus is mainly caused by insulin resistance and insulin deficiency. Due to impaired action of insulin and lack of secretion of insulin there is imbalance d metabolism of glucose. Different microvascular and macrovascular complications are due to cellular damage from chronic hyperglycemia resulting from impaired metabolism of glucose [2]. It occurs usually at advanced age above the age of 40 years. However sometimes it can start at early age. Different lifestyle factors have an impact on its development like lack of physical exercise, eating fast food, obesity etc. Treatment primarily consists of dietary modifications and physical exercise. But once

these measures are unable to control blood sugar adequately then drug therapy is initiated. Most commonly used drug is Metformin. Metformin is a biguanide group of drug. It is used as first line therapy of type 2 diabetes mellitus patients [3]. For type 2 diabetes mellitus Metformin is the drug till it alone is able to keep glycaemic level within normal limit. However with metformin only many patients with T2DM remain inadequately managed, which results in progressively declining glycemic control [4]. When Metformin alone is not able to control blood glucose level properly then additional drug is to be added. The use of additional drug must be judicial. It is dependent on the level of hyperglycaemia as well as its type. Hyperglycaemia may be baseline (fasting) or after taking food (post-prandial) or both. Drug therapy for treatment of fasting and post prandial hyperglycaemia control is different and accordingly drug is chosen. Overall glycaemic control is monitored by testing level of glycosylated haemoglobin (HbA1c). It should be below 7%. Alpha glucosidase inhibitor, dipeptidyl peptidase 4 (DPP 4 inhibitor) are some of the drugs which are mainly capable of reducing postprandial blood sugar (PPBS). But they are also capable of reducing overall glycaemic level. So, HbA1c is reduced with these two. The present study was aimed to find out the comparative ability to reduce glycosylated haemoglobin (HbA1c) with voglibose (one alpha glucosidase inhibitors) and teneligliptin (DPP 4 inhibitor).

Materials and Methods

Type of study

It was a hospital based interventional longitudinal study.

Study area

All patients giving informed consent attending General Medicine OPD of ICARE Institute of Medical Sciences and Research with diabetes and on Metformin monotherapy with uncontrolled hyperglycaemia were included in the study till the required sample size is achieved.

Sample size

Percentage of patients requiring additional anti-diabetic medication over Metformin monotherapy is 38% [5, 6]. So prevalence of use of additional drug in treating Type 2 DM (p) is 38%=0.38

So, (1-0.38)=0.62 is the number of patients not requiring additional drug over metformin (q).

If we allow error of 10% (L)

So, using the formula

$4pq/L^2$= (4*0.38*0.62)/(0.1*0.1)=94

So, required sample size is 94.

Considering 10% patients would be lost to follow up or discontinue the drug due to different reason, total required sample is 94*1.1=103.4. So, 104 patients were included in the study.

Sample design

About 52 patients were included in each arm: voglibose-metformin combination therapy and teneligliptin-metformin combination therapy. The selection of patients in each arm was done by randomization using lottery method.

Study Technique

Patients were randomized in two groups. One group received teneligliptin 20mg twice daily in addition to metformin and the other group received Voglibose 0.3mg thrice daily in addition to metformin. HbA1c was assessed before introduction of additional drug and 12 weeks after starting additional drug.

Inclusion Criteria

- Persons having inadequate glycaemic control with HbA1c above 7% but below 10%
- Persons on metformin monotherapy
- Type 2 diabetes mellitus
- Ambulatory patients
- Patients having PPBS above 200mg/dl
- Patients who can be followed up

Exclusion Criteria

- Type 1 Diabetes mellitus
- Isolated rise of fasting blood sugar (FBS)
- Non ambulatory patients
- HbA1c above 10%

Institutional ethics committee permission was taken and written informed consent was signed from each participants. Statistical test done was unpaired t test.

Results

It was a hospital based longitudinal interventional study among patients attending General Medicine outpatient department (OPD) of a Medical College, East Medinipur, West Bengal with uncontrolled hyperglycemia and whose HbA1c was above 7 but up to 10% and PPBS above 200mg/dl. Table 1 shows demographic clinical and laboratory characteristics of study participants. It shows that there was no significant difference between the baseline characteristics of two groups considering their age, sex, presence of co-morbidities, fasting and post-prandial blood sugar level (FBS and PPBS level). Figure 1 shows the mean level of glycosylated haemoglobin (HbA1c) before starting additional drug. There were two study groups. Group 1 received voglibose and group 2 received teneligliptin. Mean HbA1c level of Group 1 was 8.89% and of Group 2 was 8.83%. There was no significant difference between mean HbA1c

level between these two groups. Figure 2 shows mean level of HbA1c12 weeks after starting additional drug. For Group 1 it was 7.4% and for Group 2 it was 6.6%. Now the difference between these two is statistically significant ($p<0.05$) which indicates that people belonging to Group 1 were having significantly higher level of HbA1c than people belonging to Group 2. So after completion of 12 weeks therapy with additional drug, people receiving teneligliptin had significant lower level of HbA1c than people receiving voglibose. Figure 3 shows the change of level of HbA1c with these two additional drugs by a line diagram. The starting point is before adding additional drug and end point is after 12 weeks of continuing additional drug. It was seen that with both drugs the level of HbA1c have decreased. It was further noticed that the change of HbA1c with voglibose was less than change of HbA1c with teneligliptin. This difference was also found to be statistically significant with $p<0.05$. Statistical test done was unpaired t test.

Table 1: Demographic clinical and laboratory characteristics of study participants

Patients characteristics	Voglibose group	Teneligliptin group	P value
Age			
<60 years	36	39	>0.05
>60 years	16	13	
Sex			
Male	25	28	>0.05
Female	27	24	
BMI	27.5±4.1kg/m^2	27.1±4.4kg/m^2	>0.05
FBS	198±25.8 mg/dl	199±27.4 mg/dl	>0.05
PPBS	296±35.2 mg/dl	288±32.8 mg/dl	>0.05
Presence of co-morbidities			
Hypertension	17 (33%)	19 (37%)	
Dyslipidaemia	14 (27%)	13 (25%)	
CV events	4 (8%)	5 (10%)	

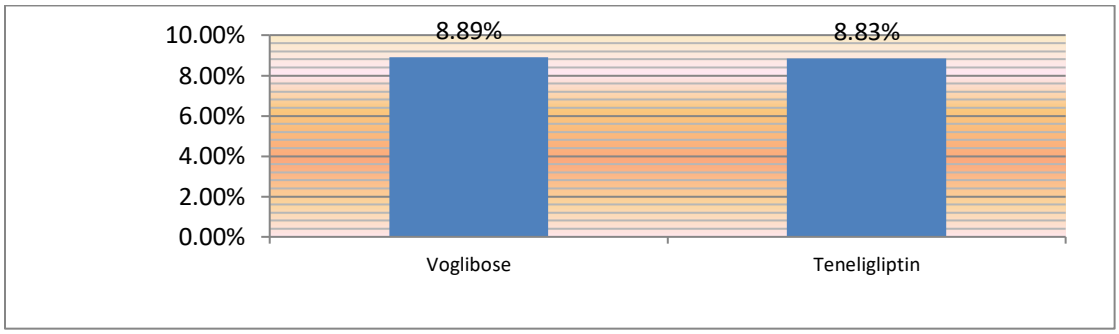

Figure 1: Mean level of HbA1c before starting additional drug

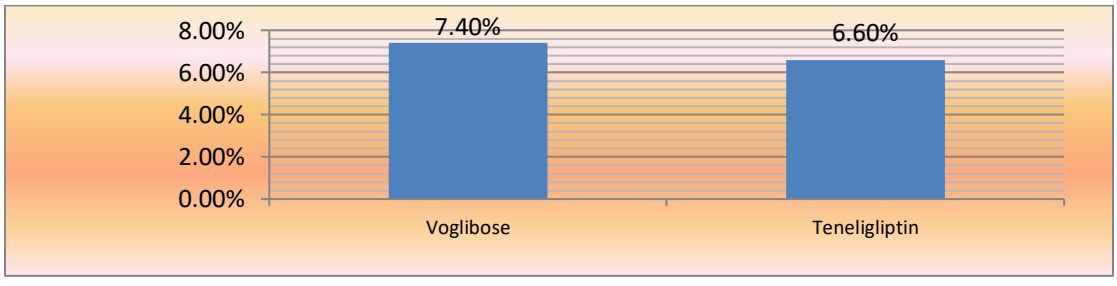

Figure 2: Mean level of HbA1c12 weeks after starting additional drug

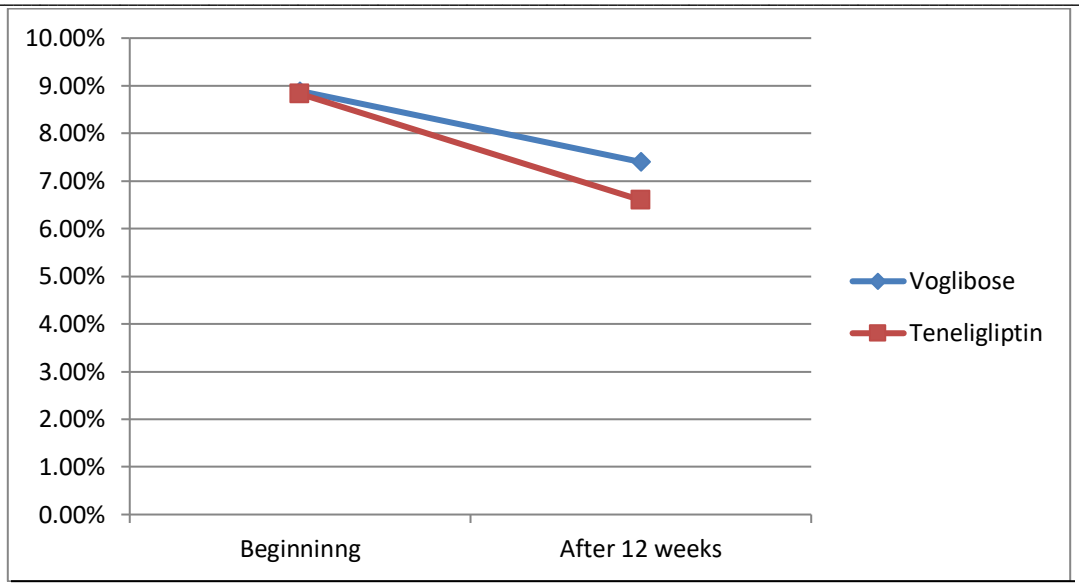

Figure 3: Change of mean HbA1c level with additional drug

Discussion

Glycosylated haemoglobin (HbA1c) gives an overall picture of glycaemic control of past three months (12 weeks). Target HbA1c should be within 7%. Recent studies suggest that very tight glycaemic control is often not beneficial and sometimes detrimental for overall prognosis of a diabetic patient [7-9]. Rather HbA1c between 6.5% and 7% should be beneficial for long term prognosis and preventing complications of diabetes. If HbA1c persists above 7% then that indicates inadequate glycaemic control which is also detrimental and promotes different microvascular and macrovascular complications of diabetes. Tight glycaemic control is often required in different acute conditions including infection and sepsis [10-12]. So maintenance of optimum level of HbA1c is essential [13-14]. Drugs should be adjusted in such a way and such a combination so that HbA1c should persist between 6.5% and 7%.

Different studies have been conducted worldwide on comparative efficacy of different DPP4 inhibitors with voglibose. However head to head study between teneligliptin and voglibose is very less. In a study conducted by Dabhi AS et al it was seen that with voglibose 0.2mg TDS dose mean change of HbA1c was -0.38+- 0.04% as compared to -0.95 +- 0.04% in group treated with vildagliptin 50mg BD [15]. Endpoint HbA1c of <6.5% was also achieved by much lower percentage of patients in voglibose group than Vildagliptin group (24% compared with 51%). Another study by Iwamoto Y et al also finds superiority of vildagliptin over voglibose in reducing HbA1c [16]. Similarly another study by Matsushima Y et al highlights superiority of sitagliptin over voglibose [17].DPP-4 inhibitors work in a glucose dependent manner, so they are able to lower HbA1c level significantly with minimum chance of hypoglycemic episode. As a result after the introduction of sitagliptin in 2006, the first DPP4 inhibitor, the use of DPP4 inhibitors is increased remarkably. Mostly they are used as add on therapy to metformin or sulfonylurea. Among all DPP4 inhibitors sitagliptin was first approved in 2006. Gradually more and more DPP4 inhibitors were developed [18]. But one of the major restricting factors of their use is their cost. Due to high cost of DPP4 inhibitors poor patients often are unable to continue these for long time. Unlike other DPP4 inhibitors teneligliptin has much lower cost. So in rural India its use is popular considering its compliance among poor patients. Teneligliptin which is classified as peptidomimetic has a unique structure having five consecutive rings [19]. So it acts on S2 extensive subsite of DPP4 and this interaction increases its potency and selectivity [20, 21]. Based on the results of a few head-to-head trials or meta-analyses comparing the efficacy between DPP-4 inhibitors, there is general consensus that the HbA1c-lowering effects of gliptins are broadly similar [22, 23].Voglibose belongs to class of comparative alpha glucosidase inhibitors which was discovered in 1981 [24]. Voglibose causes reversible inhibition of membrane bound intestines alpha glucosidase which hydrolyze oligosaccharides and disaccharides to glucose and other monosaccharides in the brush border of small intestine. So voglibose delays the absorption and digestion of dietary polysaccharides

by reversibly inhibiting carbohydrate digestive enzymes like sucrose, maltose, zomaltose etc ultimately resulting in reduction of PPBS as well as HbA1c. Teneligliptin is able to lower the PPBS as well as HbA1c significantly in 4 weeks compares to placebo. Teneligliptin 20mg OD is found to be more potent than voglibose 0.2mg TDS [25]. Many new drugs have been developed in DPP4 inhibitor class and their efficacy studied in detail [26-30]. But head to head study between efficacy of cheapest and widely used DPP-4 inhibitor in India, i.e. teneligliptin versus voglibose is lacking.

Conclusion

Many new drugs have been developed in DPP-4 inhibitor class and their efficacy studied in detail. But head to head study between efficacy of cheapest and widely used DPP-4 inhibitor in India, i.e. teneligliptin versus voglibose is lacking. The present study highlights the overall HbA1c lowering effect of teneligliptin 20mg BD is more than voglibose 0.3 mg TDS. But both drugs lower PPBS as well as HbA1c level significantly over metformin monotherapy.

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Source of Support:Nil
Conflict of Interest: Nil