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Impact of High Dose Metformin Versus Teneligliptin as add together on to Metformin on Glycemic Control of T2DM Patients

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Hyperglycaemia and abnormalities in simple carbohydrate, fat and protein metabolism are the characteristic feature of the metabolic disorder, Diabetes Mellitus. Diabetes mellitus treatment is achieved by modifications in diet, sleep pattern, regular physical activity followed by addition of anti-hyperglycemic drugs like metformin if HbA1C levels stays more than 7.0%. The study period was from April 2019 – September 2019. The total duration of study was 24 weeks. Total 160 patients were screened; among them 100 participants were selected as per the inclusion criteria. Out of 100 patients, only 91 patients have completed the study. To conclude DPP-4 inhibitor Teneligliptin 20mg OD exemplifies to be a pertinent add-on to Metformin 500mg BD to enhance the glycaemic control and could be an operative and reliable medication preference in T2DM through decent patient acceptability.

Keywords: Metformin Monotherapy; Metformin Dual Therapy; Teneligliptin; T2DM.

Hyperglycaemia and abnormalities in simple carbohydrate, fat and protein metabolism are the characteristic feature of the metabolic disorder, Diabetes Mellitus. It may result in acute and chronic vascular complications.[1] WHO estimates this metabolic disorder as the seventh most important cause of mortality in 2016. The number is anticipated to grow up to 642 million by 2040. Around 5 million people with diabetes were noted to have mortality burden. Highest death reports were reported due to Diabetes in India, the US, the People's Republic of China, and the Russian Federation in the year 2015 (IDF, 2015). Major organs affected by Diabetes are heart, kidney, nerves and eyes and problems due to hyperglycemia are crucial trigger for morbidity (IDF, 2015). In the year 2015, cause of mortality between the age group 20 to 79 years were one death in every 6 seconds and globally it accounts for 5 million people due to this disease.

Diabetes mellitus treatment is achieved by modifications in diet, sleep pattern, regular physical activity followed by addition of anti-hyperglycemic drugs like metformin if HbA1C levels stays more than 7.0%. 2 Most of the patients who were just alarmed on their pre diabetic status and who were on metformin monotherapy, shows no improvement in glycemic control on subsequent visits and progressed to combination therapy. A novel group of oral anti-hyperglycemic medications, Dipeptidyl peptidase (DPP)-4 inhibitors have displayed active progression of

function of ß cells and/or regeneration of tissues of islet cells.3 Owing to the harmonizing feat of drug mechanism, a dual therapy of metformin with a DPP 4 inhibitor declines insulin resistance, recovers the beta cell function and this facilitates in keeping HbA1C in the reference limit.[2]

Teneligliptin, described by a noticeably unyielding assembly fashioned by penta sequential rings, exists as a new-found dipeptidyl peptidase-4 (DPP-4) inhibitor for the therapy of T2DM. The piperazine moiety 1-(1-phenylpyrazol-5-yl) introduction (anchor lock domain), which muddles to the S2 wide-oscillating subsite, amplified the bustle by 1500-fold over the consistent fragment that fixes to S1 and S2 only. The clearance of the metabolites of this group is mainly through liver and kidney. As the breakdown products clearance (66%) through hepatic and (34%) through renal routes, dose correction is unwarranted for patients with renal malady. Mainly due to its prolonged t1/2, the medication has got constant glucose variations during the daytime.

Metformin an oral anti hyperglycemic drug employed in the treatment of T2DM has vital role in lowering glycosylated hemoglobin (HbA1c) levels. Teneligliptin a new DPP 4 inhibitor was also established to be effective in glycemic lowering efficacy without drastically lowering the blood glucose level (hypoglycemia) and maintains weight without any weight gain. Previous studies established the fact that a reduction of 1% HbA1C level will reduce the risk of retinopathy, nephropathy, neuropathy, and coronary artery disease which is the foremost cause of death in diabetes Mellitus patients.

Hence this research was undertaken to compare the impact of high dose metformin monotherapy against Teneligliptin with metformin combination therapy on glycaemic control of T2DM patients and to compare its adverse profile.

MATERIALS AND METHODS

Prospective, randomized, open labelled, cross-sectional study comparing the effects of Metformin 850mg BD versus Teneligliptin 20mg OD with Metformin 500mg BD in patients suffering with T2DM.This research study was conducted in patients suffering from T2DM, attending the outpatient General Medicine Department in Diabetic clinic of Sree Balaji Medical College and Hospital, Chromepet, Chennai. The research was done from April 2019 – September 2019. The entire duration of research was 24 weeks.

Criteria

The inclusion criteria of this study are Males and Females between the age 18 – 65 years, Patients who are eligible and able to participate and can give informed consent, Patients already on Metformin monotherapy and with Glycosylated Haemoglobin (HbA1c) in the range of 6.5% to 9.0%.

The exclusion criteria of this study participants includes patients who are having other type of Diabetes Mellitus patients (Type 1, Gestational) ,Patients with Glycosylated Haemoglobin (HbA1c) of > 9.0%, Pre-existing cardiovascular disease, renal dysfunction, and Hepatic disease, Patients who were on Insulin and other oral anti diabetic agents. Participamts who are Pregnant / Lactating women/Uncontrolled Hypothyroidism / Uncontrolled Hypertension/ Uncontrolled Diabetes Mellitus.

Study Procedure

This study "To compare the impact of Metformin 850mg BD versus Teneligliptin 20mg OD with Metformin 500mg BD on HbA1C in T2DM patients at a Tertiary care hospital" was conducted in compliance with the protocol, after getting approval from the Institutional Ethics Committee (IEC) with a Ref. No. 002/ SBMC/2018/1151 in Sree Balaji Medical College and Hospital, according to informed consent regulations and the ICH/GCP Guidelines.

Total 160 patients were screened, among them 100 participants were selected as per the inclusion criteria and in detail they were explained about the study pattern, possible risks, and benefits of study drugs. After explaining the protocol, write down Informed consent taken from every one of the research contributors in their local language before enrolling into the trial. They were given confidence that any retirement from the research would not affect their impending treatment in this Institution. Patients were also made to undergo Baseline investigations before enrolment for the research study. After completion of screening, all details about each patient were maintained in Case record forms and kept with the investigator.

Out of 100 patients, only 91 patients

have completed the study. In high dose Metformin monotherapy group 7 patients did not complete the study, out of which 3 patients withdrawn due to uncontrolled blood sugar level and 4 patients lost to follow up. In Teneligliptin 20mg OD+ Metformin 500mg BD group 2 patients did not complete the study, out of which 1 patient lost to stick on to treatment follow up and 1 patient retired from the study due to uncontrolled blood sugar.

Randomization

The study subjects were randomly allocated using Simple block randomization method to either of the groups Group 1 and Group 2, each group consisting of 50 patients.

Dosage Regimen

Study Group 1:

Tab. Metformin 850 mg BD orally for 24 weeks (6 months).

Study Group 2:

Tab. Metformin 500mg BD + Tab. Teneligliptin 20 mg daily single dose orally for 24 weeks (6 months).

Glycosylated Haemoglobin (HbA1c) was done at baseline, at 12 weeks and at 24 weeks. The drug was continued after the duration of study in accordance with physician's discretion.

The following investigations were done during the study period:

Blood tests were done to check Glycosylated Haemoglobin (HbA1c) at baseline, at 12th week, at 24th week.

Adverse Events

Adverse events were observed and the complaints by the study participants were mentioned according to the severity and a relativity to the study medication.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 23.0 were used for analysis of data. Mean, Standard deviation (SD) was used for continuous variables and Independent students't'-test for its comparison . All categorical variables were expressed as percentages. Categorical variables were compared and evaluated by Chi square test. "p value" of less than 0.05 was considered as statistically significant.

Observations And Results

Basic Demographic Comparision

Gender and Age distribution among the groups

The demographic data was collected and evaluated. Out of 91 patients suffering from T2DM, males were predominant with 51.6% when it is compared to females 48.4%, The descriptive statistics for age is 45.93±7.37, Table 1.

The gender comparison was done between Metformin (M) administered group and Teneligliptin with Metformin group (M+T). When both groups of data were compared, the males were predominant in Teneligliptin with Metformin (M+T) group (54.2%) whereas females were predominant in Metformin (M) group (51.2%).

Table 1. Age Descriptive Statistics

Number of participants	Minimum age	Maximum age	Mean age	S.D
Age in Years 7.372	91	32	64	45.93

Table 2. Comparison of Glycosylated Haemoglobin (HbA1c) between the Groups (Unpaired t-test)

Time/ Groups		Numberof Participants	Mean HbA1C	S.D	t-value	*p*-value
Baseline	M	43	7.63	0.50	1.962	0.053 #
	M+T	48	7.83	0.51		
12th week	M	43	7.47	0.51	0.637	0.526 #
	M+T	48	7.54	0.47		
24th week	M	43	7.27	0.45	1.845	0.068 #
	M+T	48	7.10	0.42		

Statistical Significance Nil at $p>0.05$ level

The mean age between Metformin (M) group and Teneligliptin with Metformin (M+T) group were 46±8.21 and 46±6.6, and when compared by unpaired 't' test the data was not statistically significant, as the sample selection was done randomly for the cross-sectional study.

History comparison between 2 groups

The patients who are known Diabetes was sketched out in a detail between Metformin (M) administered group and Teneligliptin with Metformin group (M+T) and the data was evaluated by Chi-square test. The Metformin (M) group with no history of T2DM were 37.2% and Metformin with Teneligliptin (M+T) group was 31.3%, similarly the Metformin (M) group with history of T2DM was 62.8% whereas Teneligliptin with Metformin group was 68.8%.

Patient's history with the other medication was taken. The Metformin (M) group with history of other medications were 27.9% and Teneligliptin with Metformin (M+T) group was 33.3%, similarly the Metformin (M) group with no history of other medications was 72.1% whereas Teneligliptin with Metformin (M+T) group was 66.7%. When it was compared by Chi-square test, the data was not statistically significant.

Glycosylated haemoglobin (HbA1c) comparison between both the groups

The glycosylated haemoglobin A1C (HbA1c) was taken from baseline with an interval of 12, 24 weeks. When the data was evaluated by unpaired t test, the baseline glycosylated haemoglobin A1C level for Metformin (M) group was 7.63±0.50 whereas for Metformin with Teneligliptin (M+T) group was 7.83±0.51 and it was not statistically significant. The glycosylated haemoglobin A1C level at 12th week for Metformin (M) group (7.47±0.51) and Metformin with Teneligliptin (M+T) group (7.54±0.47) and when it analysed was not significant. The glycosylated haemoglobin A1C level at 24th week for Metformin (M) group (7.27±0.45) and Metformin with Teneligliptin (M+T) group (7.1±0.42) and when it analysed was not statistically significant (Table 2).

Therefore, HbA1c efficacy shows more consistent significant enhancement (improvement) in Metformin with Teneligliptin (M+T) group than high dose Metformin (M) group with mean change of glycosylated haemoglobin A1C from baseline 7.83±0.51 and 7.63±0.50 to end of study period 7.1±0.42 and 7.27±0.45 respectively.

Adverse effects observed between both the groups

Adverse effects between both the groups were compared at each visit 4 weeks, 12 weeks, and 24 weeks. At the end of study period Metformin (M) group has 12(13%) patients with gastrointestinal disturbances and Metformin +Teneligliptin (M+T) has 9(9%) patients with gastrointestinal disturbances (7 patients) and nasopharyngitis (2 patients).

DISCUSSION

This research revealed that the prevalence of T2DM was greater in males than in females. The males were higher in Metformin + Teneligliptin group (54.2%) whereas females were higher in Metformin group (51.2%). As per the previous research carried out by Bennett et al 4and Sharma et al5 T2DM incidence among men was higher than women which is consistent with our study. The mean age between Metformin (Group 1) and Teneligliptin + Metformin (Group 2) were 46±8.21 and 46±6.6 respectively. This study showed a history of T2DM in 65.9 % of patients. T2DM has significant relation with family history; if any one or both parents had T2DM it can be transferred from one generation to another at one point in their life. This was also similar with Bennett et al.'s wider prospective study.4 In this research, the average Diabetes Mellitus period was 0–10 years, which is parallel with the Jeon et al research.[6]

At the end of study period (24 weeks), high dose Metformin group has showed the following results, mean change of HbA1c were reduced from 7.63±0.50 to 7.27±0.45 respectively whereas in Metformin and Teneligliptin combination therapy, the results were mean change of glycated haemoglobin (HbA1c) were significantly decreased from 7.83 ± 0.51%, to 7.10±0.42%, respectively. The results are perfectly showing consistent significant improvement of HbA1C with the Teneligliptin + Metformin group when compared to a Metformin group from starting (baseline) to the end of (24 weeks) study period. Although high dose Metformin monotherapy shows decrease in HbA1C, it is lesser than the Metformin + Teneligliptin group as depicted in previous studies.

Recently Batta Raghuveer et al., was done another study to access the effectiveness of Teneligliptin with metformin in T2DM patients. The effectiveness was evaluated by measuring the mean change in the glycated haemoglobin (HbA1c) levels at the end of 24 weeks. The combination therapy of Metformin with Teneligliptin was shown a clinically significant improvement in HbA1C values. This study described that Teneligliptin is an effective add on drug in uncontrolled T2DM patients with metformin monotherapy.[7]

DPP-4 inhibitor, Teneligliptin were tried in numerous populations of T2DM as monotherapy or with other anti-diabetic agents as combination therapy.[8,9-13] These studies comprised both short, long-period studies from twelve to fifty-two weeks and get stated a substantial decrease in blood sugar level with an improvement in HbA1c (glycosylated Haemoglobin) of 0.8% to 0.9% reduction in three months (12 weeks), was continued up to fifty-two weeks of Teneligliptin treatment.[8,9-13]

Adverse effects were compared and analysed, about 13% and 10% were reported in Metformin and Teneligliptin + Metformin group respectively. No critical harmful effects were registered in any of the groups.

In our research, both the study drugs show improvement in their glycaemic profile, and it has additional pleiotropic effects. Therefore, DPP-4 inhibitor Teneligliptin 20mg OD with Metformin 500mg BD shows significant improvement when compared to high dose Metformin 850mg BD monotherapy in T2DM patients which is in consistence with previous studies.

CONCLUSION

To conclude DPP-4 inhibitor Teneligliptin 20mg OD exemplifies to be a pertinent add-on to Metformin 500mg BD to enhance the glycaemic control and could be an operative, reliable medication preference in T2DM as well as decent patient acceptability.

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Conflicts of Interest

There is no conflict of Interest.

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