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AN OBSERVATIONAL STUDY OF METFORMIN AND COMBINATION OF METFORMIN AND SITAGLIPTIN IN TYPE II DIABETIC MELLITUS PATIENTS.

Pharmacology

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ABSTRACT

Introduction-Metformin is used in the treatment of type II diabetes mellitus and addition of Sitagliptin with Metformin may improve glycaemic control.

Aim-To compare the efficacy and safety of Metformin alone and combination of Metformin and Sitagliptin in type II mellitus patients.

Material and methods-It was observational study on 50 patients each in metformin group and metformin with sitagliptin group. After enrolment in study follow up was done at 4,8 and 12 weeks of therapy.

Result-At 4 and 12 weeks reduction in fasting plasma glucose significantly ($p<0.05$) more in Group II than in GroupI but reduction at 8 weeks is statistically nonsignificant ($p>0.05$); while reduction in postprandial plasma glucose at 4,8 and 12 weeks significantly ($p<0.05$) more in Group II than Group I.

Conclusion- In patients who had inadequate glycaemic control with Metformin alone, the addition of Sitagliptin was more efficacious and well tolerated.

KEYWORDS

Metformin., Sitagliptin , TypeII diabetes mellitus.

INTRODUCTION

The term "diabetes" was first used by Greek Appolonius of Memphis which means "to pass though".It was Briton John in late 1700s who added the term "mellitus" meaning "from honey", distinguishing diabetes insipidus from diabetes mellitus, the former is associated with frequent urination without hyperglycemia. The treatment for diabetes mellitus was discovered in 1921 by two Canadians Frederick Banting& Charles.[1]A Metabolic disorder, type II diabetes mellitus is characterized by hyperglycemia which is caused by either insulin resistance or insulin deficiency.[2]Type II diabetes mellitus accounts for more than 90% of all diabetes mellitus. [3] The prevalence of diabetes mellitus is 2.4% in rural and 11.6% in urban India and 6% in world.[4] As diabetes mellitus is a serious problem both in rural and urban areas of our country, a study should be done to evaluate the most potent and efficient drug.

To treat type II diabetes mellitus, metformin is the most effective oral medication. Metformin via its inhibitory action on gluconeogenesis in liver is known to improve glycaemic control and improvement in uptake of glucose.[5] The group of metabolic hormones "Incretins" released after eating stimulate synthesis of insulin and glucagon from pancreatic beta and alpha cells respectively, which trigger the level of blood glucose to fall.[6]Glucagon like peptide -1 (GLP-1) and gastrin inhibiting peptide(GIP) are inhibited by enzyme Dipeptidyl peptidase (DPP-4),which are incretins that stimulate insulin secretion. DPP-4 inhibitors enhance levels of the active incretins hormone, that are released in the circulation after digestion of meal. Majority of action of incretins is accounted by GLP-1.GLP and GIP increase insulin release and thereby decreasing the post meal rise in glucose concentration and reducing fasting glucose concentration.New class of antidiabetic agents DPP-4 inhibitors improves glycaemic control by reducing both fasting and post prandial levels without weight gain has been developed for patients of type II diabetes mellitus.[7]. Sitagliptin is a low molecular weight pyrazine phosphate that selectively and competitively inhibits the enzyme DPP-4.By blocking inactivation of incretin,sitagliptin increases active incretins levels increase which helps in the treatment of type II diabetes mellitus patients with this new approach.Sitagliptin has a long half life allowing for once daily and is indicated for use in patients with type II diabetes mellitus. Because Sitagliptin and Metformin target potentially complementary pathway, the addition of Sitagliptin with Metformin may improve glycaemic control.

Metformin is frequently used in treatment of type II diabetes mellitus and despite its proven efficacy, plasma glucose remain uncontrolled with monotherapy.[8]As the disease is progressive in nature, additional agents were required in line of treatment to maintain glycaemic control.An alternative approach of combination therapy was proposed to achieve the goal of maintaining glycaemic control and delaying the need of any subsequent regimen of treatment. [9].The present study was planned with the aim to analyze efficacy and safety of Metformin alone and combination of Metformin and Sitagliptin in inadequately controlled with metformin alone in type II diabetic mellitus patients.

MATERIAL AND METHODS

The Study was carried out in tertiary care hospital and institutional ethical committee approval was obtained before starting the study. This was Prospective Observational Study.100 type II diabetes mellitus patients were included in the present study as per the selection criteria after receiving their informed consent. Patients were divided to Group I and Group II.The Group I comprised of patients receiving Metformin (500mg orally twice daily), while Group IIcomprised of patients receiving of combination of Metformin (500mg orally twice daily) and Sitagliptin(100mg orally once in a day).Sitagliptin was added in type II diabetic patients which were inadequately controlled with metformin alone.The following categories of patients were enrolled in the study : (1)Type II diabetes mellitus patients without any comorbidity.(2) Patients not on drugs which cause either hypoglycemia or hyperglycemia.The following categories of patients were excluded from the study; (1) Patients with type I diabetes mellitus .(2) Patients not willing to give consent.Baseline Fasting(FPG) and post-prandial plasma glucose (PPPG) levels were measured . Follow up was done at 4, 8 and 12 weeks of therapy. At each visit, FPG Level and PPPG level were measured and safety of drugs were noted.

STATISTICS

The continuous variables were presented as Mean ± SD, and the difference in the means were analyzed by unpaired students 't' test and categorical data was analyzed using chi-square test.'p' value of <0.05 was taken as significant and 'p' value <0.0001 was taken as highly significant.

RESULTS

Total 100 patients suffering from type II diabetes mellitus were selected in the present study. The mean age of the patients

was53.96±10.70 years in Group I and 54.36±11.61 years in Group II. Male to Female ratio was 56:44 (56% versus 44%). (Table No.1)

In Group I baseline mean FPG was 140.56±55.59 mg/dl.After treatment with metformin the FPG was reduced to 135.05±45.05,137.95±38.34 and 131.62±44.62 at 4,8and 12 weeks respectively. The reduction in mean FPG was not significant statistically (p>0.05). (Table No.2)

In Group II baseline mean FPG was 164.70±59.87mg/dl.After treatment with combination of metformin and sitagliptin the FPG was reduced to 156.06 ±55.94,141.60±50.29 and 118.80 ±33.92 at 4,8and 12 weeks respectively. The reduction in mean FPG was statisticallynon-significant(p>0.05) at 4 weeks but statistically significant (p<0.05) at 8weeks and statistically highly significant (p<0.0001) at 12 weeks.(Table No.2)

In Group I baseline mean PPPG was 203.84±77.79mg/dl. After treatment with metformin the PPPG was reduced to 196.02±70.67, 195.80±63.02 and 186.08 ±61.24 at 4,8and 12 weeks respectively. The reduction in mean PPPG was not significant statistically (p>0.05) at 4,8 and 12 weeks. (Table No.3)

In Group II mean baseline PPPG level was 224.70±83.18mg/dl.After treatment with combination of metformin and sitagliptin the PPPG was reduced to 221.64±80.46,199.28±75.22 and 166.98 ±50.26 at 4,8 and 12 weeks respectively. The reduction in mean PPPG by combination of metformin and sitagliptinwas not significant statistically (p>0.05) at 4 and 8weeks but statistically highly significant (p<0.0001) at 12 weeks. (Table No.3)

The mean values of FPG in Group I and Group II were 135.05 ±45.05 and 156.06 ±55.94, 137.95±38.34 and 141.60±50.29, 131.62 ±44.62 and 118.80 ±33.92 respectively at 4,8and 12 weeks. On comparison of reduction in FPG between both the groups, the reduction was found to be significant (p<0.05) at 4 &12 weeks but was not significant (p>0.05) at 8 weeks.The percent reduction in FPG in Group I was noted to be 3.92%,1.85% and 6.38% at 4,8 and 12 weeks respectively and the percent reduction in FPG in Group II was found to be 5.24%,14.02% and 27.86% at 4,8 and 12 weeks respectively. (Table No.4)

The values of mean PPPG in Group I and Group II was 196.02±70.67 and to 221.64±80.46, 195.80±63.02 and 199.28±75.22, 186.08 ±61.24 and 166.98 ±50.26 at 4,8 and 12 weeks respectively. On comparison of reduction in PPPG in both the groups, the statistically significant (p<0.05) difference was found at 4 and 12 weeks but non-significant (p>0.05) at 8 weeks.The percent reduction in PPPG Group I was noted to be 3.83%,3.94% and 8.71% at 4,8 and 12 weeks respectively. The percent reduction in PPPG in Group II was found to be 1.36%,11.31% and 25.68% at 4,8 and 12 weeks respectively. (Table No.5)

Table 1: Age and sex-wise comparison between the Group I and Group II

Characteristics		Group I (n=50)	Group II (n=50)	p value
Age (Years)		53.96 ± 10.70	54.36 ± 11.61	>0.05
Gender	Male	26	30	>0.05
	Female	24	20	

Table 2: Comparison of metformin monotherapy and combination of metformin & sitagliptin on Fasting Plasma Glucose level in mg/ dl at 0,4,8 and 12 weeks

Time interval	Group I (Mean± SD)	p value	Group II (Mean± SD)	p value
Initial Level (0 Week)	140.56 ± 55.59		164.70 ± 59.87	
4 Weeks	135.05 ± 45.05	>0.05	156.06 ± 55.94	>0.05
8 Weeks	137.95 ± 38.34	>0.05	141.60 ± 50.29	<0.05*
12 Weeks	131.62 ± 44.62	>0.05	118.80 ± 33.92	<0.001*

*statistically significant

Table 3: Comparison of metformin monotherapy and combination of metformin & sitagliptin on Postprandial Plasma Glucose level in mg/dl at 0,4,8 and 12weeks

Time interval	Group I (Mean± SD)	p value	Group II (Mean± SD)	p value
Initial Level (0 Week)	203.84 ± 77.79		224.70 ± 83.18	
4 Weeks	196.02 ± 70.67	>0.05	221.64 ± 80.46	>0.05
8 Weeks	195.80 ± 63.02	>0.05	199.28 ± 75.22	>0.05
12 Weeks	186.08 ± 61.24	>0.05	166.98 ± 50.26	<0.001*

*statistically significant

Table 4: Comparison of changes in Fasting Plasma Glucose level in mg/dl at 0, 4, 8 and 12 week in Group I and Group II

Time interval	Group I (Mean± SD)	Percentage reduction in initial level	Group II (Mean± SD)	Percentage reduction in initial level	p value
Initial Level (0 Week)	140.56 ± 55.59	-	164.70 ± 59.87	-	< 0.05
4 Weeks	135.05 ± 45.05	3.92%	156.06 ± 55.94	5.24%	<0.05*
8 Weeks	137.95 ± 38.34	1.85%	141.60 ± 50.29	14.02%	>0.05
12 Weeks	131.62 ± 44.62	6.38%	118.80 ± 33.92	27.86%	<0.05*

*statistically significant

Table 5: - Comparison of changes in Postprandial Plasma Glucose Level in mg/dl at 0,4,8 and 12 weeks in Group I and Group II.

Time Interval	Group I (Mean± SD)	Percentage reduction in initial level	Group II (Mean± SD)	Percentage reduction in initial level	p value
Initial Level (0 Week)	203.84 ± 77.79	-	224.70 ± 83.18	-	>0.05
4 Week	196.02 ± 70.67	3.83%	221.64 ± 80.46	1.36%	<0.05*
8 Week	195.80 ± 63.02	3.94%	199.28 ± 75.22	11.31%	>0.05
12 Week	186.08 ± 61.24	8.71%	166.98 ± 50.26	25.68%	<0.05*

*statistically significant

Table 6: -Comparison of Adverse Drug Effects between Group I and Group II.

Adverse Effects	Group I(n=50)	Group II(n=50)
Vomiting	13(26%)	3(6%)
Abdominal pain	3(6%)	1(2%)
Diarrhea	6(12%)	2(4%)
Metallic taste	4(8%)	1(2%)

The safety analysis was performed on all patients who completed the study. A total of 52% of the patient reported adverse effects like vomiting (26%),abdominal pain (6%),diarrhea (12%) and metallic taste (8%) in the group I. Whereas a total of 14% patients reported adverse effects like vomiting (6%), abdominal pain (2%), diarrhea (4%), metallic taste (2%) in the group II. (Table No.6)

DISSCUSSION

In 2015 almost 415 million people worldwide were affected by type 2 diabetes mellitus [10] Health care budget on controlling type II diabetes mellitus consumes about 10% of total budget which resulted in reduction of rise of complications but it very difficult to achieve it [9]. In order to maintain appropriate glycaemic target there is a need to intensify therapy because type II diabetes mellitus is characterized by deterioration of glycaemic control and worsening of pancreatic function. Making dual therapy became a necessary to achieve glycaemic control because 60% of diabetic patients who were on monotherapy did not achieved their therapeutic target [11].

An approach to delay the glycaemic deterioration in patients, starting the combinational therapy at initial early stage was proposed, with outcome of preservation of functioning of beta cells. [9,12] The use of two or three drugs in combination is responsible for the improving glycaemic control with their distinct mechanism, it also result in overall drug dosing in same setting and minimize adverse effects. [13,14,15]

The present study showed that the combination of Metformin and Sitagliptin is more effective than Metformin alone in type II diabetics.

The reduction in fasting plasma at 4 and 12 weeks was higher in Group II significantly than Group I, but there was no significant reduction at 8 weeks; while reduction in postprandial plasma glucose at 4,8 and 12 weeks was significantly ($p<0.05$) more in Group II than Group I.Statistically significant reduction in percentages of mean FPG level at 4,8 and 12 weeks and mean PPPG at 8 and 12 weeks was noted in Group II patients compared to Group I patients; while reduction in mean FPG at 4 week was noted in Group I patients compared to Group II patients. Reasner et al, concluded that the efficacy of combinational therapy of metformin and sitagliptin with significant reduction in fasting as well as postprandial plasma glucose, the similar results were noted by Perez-monteverde et al and Wanstein et al.[16,17,18]Study carried out by Benard Charbonel et al showed the efficacy ofaddition of daily one dose of Sitagliptin 100mg with ongoing Metformin therapy in type II diabetic patients who had insignificant glycaemic control with monotherapy using Metformin. [19]

When patients were treated with single antidiabetic drug, they were not able to achieve and maintain glycaemic control therefore many patients required combination of antidiabetic drug [14] In the present study the improvement in glycaemic control was the key finding after addition of sitagliptinin patients with metformin monotherapy and inadequate glycaemic control.

The incidence of adverse effects was less in metformin and sitagliptin combination group. The adverse effects in group I were noted to be higher than group II patients. Benard Charbonel el at also showed that addition of single dose daily of Sitagliptin 100mg was well tolerated along with Metformin therapy in patients treated with metformin alone and having Inadequate glycaemic conrtol.[19] In a study by Reasner et al the combination therapy of metformin and sitagliptin exerted the gastrointestinal side effects in 20.6% of patients and patients on monotherapy exerted the gastrointestinal side effects in 24.6% of patients[16].

Thus in patients who are on monotherapy with metformin alone having inadequate glycaemic control, the efficient and tolerable way of maintaining glycaemic control is the addition of one daily dose of Sitagliptin 100 mg.

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