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EFFECT OF BROMOCRIPTINE QUICK RELEASE ON SERUM LIPID LEVELS IN TYPE 2 DIABETES MELLITUS PATIENTS- AN OPEN LABEL RANDOMIZED CONTROLLED STUDY.

Dr. A. Sharmila*	Associate Professor, Department Of Pharmacolgy, Kilpauk Medical College, Chennai. *Corresponding Author
Dr. Nithya Priya	Assistant Professor, Department Of Pharmacolgy, Coimbatore Medical College, Coimbatore.
Dr. E. Amudhan Arvind	Senior Assistant Professor, Department Of Pharmacolgy, Government Dharmapuri Medical College, Dharmapuri.

ABSTRACT **Objectives:** Bromocriptine Mesylate QR [Quick release] formulation was approved by FDA for management of Type 2 Diabetes mellitus[DM].Many previous works stresses the effect of Bromocriptine in decreasing the blood glucose levels. This study was intended to highlight the effect of Bromocriptine QR in serum lipid levels and body mass index [BMI] of Type 2 diabetes mellitus.

Methods: 140 patients with Type 2 DM were randomized into two groups. The control group was treated with Metformin 500mg bd [twice daily] and Glipizide 5mg bd for a period of 3 months. The study group received Bromocriptine quick release 1.6 mg once daily, Metformin 500mg bd and Glipizide 5mg bd for a period of 3 months. In both groups, body mass index and fasting lipid profile was measured at the start of the study and at the end of the study.

Results: At the end of the study, statistically significant decrease [$p<0.05$] in low density lipoprotein [LDL] and Triglycerides [TGL] was seen in study groups not in the control group. Total cholesterol decreased significantly in both study and control groups. But the decrease in total cholesterol, is higher in the study group than the control group [$p=0.001$]. There is no significant change in the High density lipoprotein [HDL], Very low density lipoprotein [VLDL] level and BMI in both control and study group when compared to baseline.

Conclusions: Bromocriptine QR when combined with Metformin and Glipizide reduced LDL, TGL, Total cholesterol significantly compared to Metformin and Glipizide in type 2 DM patients.

KEYWORDS : Bromocriptine, Total cholesterol, LDL, TGL, Type 2 DM.

INTRODUCTION

Bromocriptine, a dopamine D2 receptor agonist is an approved drug for the management of Parkinson's disease, hyperprolactinemia. Bromocriptine Mesylate QR [Quick release] formulation was acknowledged for management of Type 2 DM by FDA in 2009[1]. The plus of Bromocriptine in diabetes mellitus is they act by changing the course of central glucose and energy metabolism pathways [2].

The etiology of diabetes mellitus is multifaceted which include genetic and environmental aspect such as obesity, unfavorable diet and sedentary lifestyle [3]. As body fat enhance, insulin resistance elevate due to decrease in insulin receptors and reduction in receptor role [4].Type 2 Diabetes and obesity becomes a vicious cycle. The greater than before morbidity and mortality in diabetes patients is mostly attributed to Coronary Vascular Disease [CVD] [5]. High cholesterol values are encountered more in Diabetics than Non diabetics [6,7]. Elevated cholesterol cause atherosclerosis leading to CVD and stroke [8]. Hence managing diabetes mellitus should be intended at and achieving maintaining perfect body weight, normal lipid profile and euglycemia [9,10].

The insulin resistant state ensures glucose supply to the central nervous system by increasing hepatic glucose output and by decreasing peripheral glucose utilization[11] Animals then slip back to an insulin sensitive condition when there is abundance of food. The metabolic modifications such as insulin resistance, increased hepatic glucose output and increased lipolysis which are needed in times of fasting or famine occurs in other period also .As a consequence there is an increased blood sugar and dyslipidemia in Type 2 diabetic patients.

These changes in body weight and insulin resistance depending on season are due to changes in hypothalamic neuroendocrine rhythms [12]. Reduced dopaminergic neurotransmission is involved in the pathogenesis of obesity associated hyposomatotropism[13].Drugs with antidopemenirgic effects like antipsychotic drugs show negative effects like increased insulin resistance, dyslipidemia and weight gain. Dopamine agonists improves dopamine, which has a role in controlling metabolic effects [14]. Bromocriptine is a exclusive Oral hypoglycemic agent with central mechanism of action by resetting hypothalamic circadian rhythm .Bromocriptine reduces plasma glucose, triglycerides, FFA levels, and thus reduces cardiovascular risk. Bromocriptine alters neurotransmitter action in the brain and corrects glycemic control and insulin resistance in animal models of obesity and diabetes [15].Also Bromocriptine reduces leptin levels and leptin resistance, and produces antiobesity effect [16].

Hence, Bromocriptine, in addition to its blood glucose reducing effect, has positive effect on lipid profile and body weight has to be evaluated further for the treatment of type 2 diabetes mellitus. This study was done to probe the effect of Bromocriptine in serum lipid profile and BMI of type 2 diabetic patients. It was an open label randomized controlled study conducted at Chengalpattu Government hospital at Tamilnadu in diabetic population.

Methods

A prospective, open labeled, comparative, randomized controlled study was conducted after approval from institutional ethical committee and as per the GCP guidelines. 200 Type 2DM patients attending diabetic OPD, Department of General medicine, Government Chengalpattu medical college and Hospital, Chengalpattu were screened and 140 type 2 DM patients who fulfilled the selection criteria were recruited for the study.

Inclusion Criteria:

Both male and female patients of age 30-60 years, who are willing to give informed consent Known T2DM for more than 5 years, taking Metformin 500mg bd and Glipizide 5mg bd.

Exclusion Criteria

All cases of Type 1 DM, Pregnant & lactating women, Age< 30 years and >60 years, Patients with FBS>300mg/dl and PPBS> 400 mg/dl , HbA1C >10%.Patients in whom insulin is indicated for treatment, Patients associated with renal & liver disease, Patients with coronary arterial disease, dyslipidemia, CCF, migraine, Peripheral vascular disease, psychiatric illness Patients with- known hypertension BP> 140/90mmhg, Any concurrent intake of sympathomimetic drugs, Any other serious medical or surgical illness were excluded from the study.

After getting informed consent, around 140 diabetic patients who satisfy the selection criteria were randomly allocated in to two groups with 70 patients in each group. All the odd number patients were allocated into control group and all the even number of patients were allocated into study Group. After baseline investigations and clinical examination, the Study Group patients already on Metformin 500mg bd & Glipizide 5mg bd were added Bromocriptine 1.6mg od for a period of 12 weeks. For initial 1 week, Bromocriptine 0.8 mg OD was prescribed within 2 hrs of waking, followed by single Morning dose of

1.6 mg/day within 2hrs of awaking for next 11 weeks[17]. In the Control Group, patients already on Metformin 500mg BD & Glipizide 5mg BD are continued with the same for next 12 weeks. Patients were asked to follow the diabetic diet chart, regular exercises, and to stop smoking.

Body mass index estimation, fasting lipid profile was done at baseline at the start of the study and at the end of the study [after 12 weeks] for each patient in both study and control group. Blood pressure monitoring, baseline laboratory investigations, Patients were asked to report any adverse effects immediately to the investigator during the study period .At the end of 3 months, Patients were advised to follow their regular drugs after the study and dosage adjusted according to their blood glucose level. Bromocriptine was withdrawn, at the end of the study .Patients were monitored for any adverse effects for 2 weeks. The data from investigations were collected, tabulated and analyzed statistically. Statistical analysis was done with paired and unpaired t test. Statistical analysis of the results was done using software SPSS 22.

RESULTS

After screening 200 patients, 140 patients who satisfy the inclusion criteria were recruited for this study. Out of 140 patients, 14 patients were lost to follow up. 8 patients were withdrawn from the study due to side effects. Only 118 patients completed the study, results of those 118 patients were analyzed statistically.

At the start of the study, no statistically significant difference was seen between study & control groups in Age, sex distribution, fasting lipid profile, body mass index before drug administration. Table 1 shows BMI Distribution at the start of the study and after 3 months. No statistically significant difference between study & control groups in BMI before drug administration. At the end of the study there is a mild decrease in BMI in both control and study groups. In Control group, decrease of mean BMI is seen from baseline- 26.36 to 26.1 [0.3] after 3 months. In Study Group, decrease of mean BMI is seen from baseline - 26.03 to 26.01 [0.5] after 3 months. When paired t test was used to compare mean BMI before and after drug, the decrease in BMI in the study group and control group is not statistically significant.

Table 1: Bodymass Index Before And After The Study In Both Groups.

BMI	CONTROL		STUDY		STUDENTS INDEPENDENT t TEST
	MEAN	SD	MEAN	SD	
BASELINE	26.36	2.389	26.03	2.02	P=0.42
AFTER 3MONTHS	26.1	2.456	26.01	2.045	P=0.825
Paired T test	P=0.05		P=0.19		

Table 2 demonstrates there is no statistical difference between Total cholesterol at baseline in control and study groups. At the end of the study there is the decrease in Total cholesterol in both study and control groups. In Control group, decrease of mean total cholesterol seen from baseline- 243.22 to 241.72 [1.5] after 3 months. In Study Group, decrease of mean total cholesterol seen from baseline - 254.85 to 247.22 [7.6] after 3 months. When paired t test was used to compare mean total cholesterol before and after drug administration statistically significant reduction is seen in study group [p=0.0001] and the control group [p=0.003] at the end of the study. But the reduction is more in the study group than the control group.

Table 2: Total Cholesterol Before And After The Study In Both Groups.

TOTAL CHOLESTEROL	CONTROL		STUDY		STUDENT INDEPENDENT "t test"
	MEAN	SD	MEAN	SD	
BASELINE	243.22	44.394	254.85	27.296	P=0.085
AFTER3 MONTHS	241.72	43.985	247.22.	25.634	P=0.402
PAIRED t TEST	P=0.003		P=0.0001		

Table 3 demonstrates there is no statistical difference between LDL at baseline in control and study groups. In Control group, decrease of mean LDL was seen from baseline- 160.1 to 160.03[0.2] after 3 months. In Study Group, decrease of mean LDL was seen from baseline - 173.67 to 166.3 [7.37] after 3 months. At the end of the study, there is decrease in LDL in both study and control groups. When paired t test was used to compare mean LDL before and after drug administration, statistically significant reduction was seen in study group at the end of the study [P = 0.001]. The reduction in control group is not statistically significant [P=0.7].

Table 3: LDL Before And After The Study In Both Groups.

LDL	CONTROL		STUDY		STUDENT INDEPENDENT "t test"
	MEAN	SD	MEAN	SD	
BASELINE	160.1	35.384	173.67	26.648	P=0.019
AFTER3 MONTHS	160.03	34.329	166.3	26.626	P=0.266
PAIRED t TEST	P=0.7		P=0.001		

Table 4 demonstrates there is no statistical difference between VLDL at baseline in control and study groups. At the end of the study there is the mild decrease in VLDL in both study and control groups. In Control group, decrease of mean total cholesterol was seen from baseline- 44.68 to 43.8[0.88] after 3 months. In Study Group, decrease of mean total cholesterol was seen from baseline - 35.2 to 34.73 [0.47] after 3 months. The decrease in VLDL is not statistically significant in both groups, when paired t test was used to compare VLDL before and after drug administration.

Table 4: VLDL Before And After The Study In Both Groups.

VLDL	CONTROL		STUDY		STUDENT INDEPENDENT "t test"
	MEAN	SD	MEAN	SD	
BASELINE	44.68	23.898	35.2	9.892	P=0.006
AFTER3 MONTHS	43.8	21.812	34.73	8.986	P=0.004
PAIRED t TEST	P=0.3		P=0.2		

Table 5 demonstrates there is no statistical difference between TGL at baseline in control and study groups. At the end of the study there is the decrease in TGL in both study and control groups. In Control group, decrease of mean TGL seen from baseline- 178.9 to 177.44[1.46] after 3 months. In Study Group, decrease of mean TGL was seen from baseline - 176.15 to 166.2 [9.95] after 3 months. Paired t test was used to compare mean TGL before and after drug administration. In the study group the decrease in mean TGL is higher and statistically significant [P = 0.001].The decrease in mean TGL is not statistically significant in the control group. [P=0.06].

Table 5 : TGL Before And After The Study In Both Groups.

TGL	CONTROL		STUDY		STUDENT INDEPENDENT "t test"
	MEAN	SD	MEAN	SD	
BASELINE	178.9	26.476	176.15	34.584	P=0.674
AFTER3 MONTHS	177.44	27.023	166.2	35.773	P=0.064
PAIRED t TEST	P=0.06		P=0.001		

There is also no statistical difference between HDL at baseline in control and study groups. When paired t test was used to compare HDL before and after drug administration no statistically significant change is seen in study group as well as the control group is seen.

At the end of the study, the reduction of Mean Total cholesterol, LDL, TGL in the study group is more than the reduction seen in the control group and it is statistically significant. No statistically significant change in mean VLDL, HDL, BMI was seen in study group as well as the control group is seen. 8 patients were withdrawn from the study due to adverse effects. [3 in control group, 5 in study group]. No serious adverse effects were reported during the study. No stastically significant difference seen between the adverse effects of study and control groups.

DISCUSSION

In Diabetes mellitus, Hyperglycemia leads to glycosylation of proteins including LDL Apo proteins. Elevated cholesterol values are seen more in Diabetics than Nondiabetics[6,7].

Dyslipidemia, especially increased LDL seen in diabetic patients increases the macro vascular complications in diabetes mellitus[18]. Hence drugs which reduce blood glucose and also having antidyslipidemic effects are to be encouraged in the treatment of diabetes mellitus.

Bromocriptine when used in the treatment of diabetes mellitus throws light on the new approach in the treatment of obesity and dyslipidemia. Bromocriptine induces positive metabolic effects such as decreasing blood glucose and serum lipid profile and positive effect on bodyweight, blood pressure and cardiovascular events.Bromocriptine apart from improving glycemic control it reduces body fat stores.

More studies are needed to evaluate the effect of Bromocriptine in lipid

profile and BMI in diabetic population of Tamilnadu. Hence this study was done to evaluate the effect of Bromocriptine in lipid profile, BMI in patients with Diabetes mellitus coming to Diabetic outpatient department of Chengalpattu medical college and hospital, Tamilnadu. In this study, diabetic patients were divided in to two groups. Patients received Bromocriptine of 1.6mg in addition to Metformin and Glipizide in the study group and control group received only Metformin and Glipizide and the results were compared.

In our study, BMI measurement and fasting lipid profile was done at the start and end of the study in both study and control groups. The study results showed the decrease in BMI in the study group and control group is not stastically significant at the end of the study. In some studies the results show insignificant effect of Bromocriptine on weight, however in all studies Bromocriptine does not cause weight gain[12].

The results of our study show that there is stastically significant reduction in Total cholesterol in the study group [p=0.0001] and also in the control group. [p=0.003]. But the reduction was higher in the study group .There is stastically significant reduction in LDL in the study group [p=0.001] but not in the control group [p=0.7].There is stastically significant reduction in TGL in the study group [p=0.001] but in the control group [P=0.06] no stastically significant reduction was seen at the end of the study.

But there was no stastically significant reduction in VLDL in the study group as well as in the control group seen at the end of the study. Also there is no significant increase in the HDL level in both control and study group when compared to baseline. So there is no adverse effect of causing increase in blood lipid levels in study group and also in control group.

Previous studies by Cincotta et al., showed a stastically significant results depicting decrease in fasting and post-prandial triglycerides by 72 and 63 mg/dl ($P < 0.005$) and fasting and post-prandial free fatty acids by 150 and 165 qr/l ($P < 0.05$), compared to placebo[12]. Some other studies showed insignificant results when the effect of Bromocriptine on lipid profile is compared to placebo group[19].

Also previous studies by Ghada Mohammad Al-Ashmawy et al. showed that treatment with Bromocriptine for 8 weeks decreased body weight, BMI, TC, TGs, and LDL[16]. Also similar studies by Dos Santos Silva CM et al.: demonstrated a significant reduction in TGs and LDL with dopamine agonist treatment [20]. The same research reported non-significant differences in BMI between the dopamine agonist treatment and control groups. However some studies have reported no significant effect of Bromocriptine treatment on the lipid profile[21, 22] Several anti-diabetic drugs such as Rosiglitazone caused adverse effect on lipid profile[23]. In our study, no adverse effect on serum lipid was found to be caused by Bromocriptine.

Monitoring for adverse events also showed no major life threatening adverse effects. Mild adverse effects like nausea, vomiting and hypoglycemia occurred during the study period. There was no stastically significant difference between the adverse effects in the study and control groups. So, Bromocriptine quick release is a safe drug that can be used in type 2 Diabetes mellitus. It is available in India as tablet Bromocriptine Mesylate I.P equivalent to Bromocriptine 0.8 mg.

In summary**,** the results of this randomized open labeled clinical trial show in Type 2 Diabetes Mellitus, add on therapy of Bromocriptine QR to Metformin and Glipizide in the study group, when compared to the control group of patients receiving Metformin and Glipizide alone have caused significant reduction in the Total cholesterol, LDL, TGL. There is no significant changes in the BMI, HDL and VLDL level in both control and study group when compared to baseline. There are no serious adverse effects observed in Type 2 Diabetes Mellitus patients taking Bromocriptine QR 1.6 mg OD.

CONCLUSION:

Bromocriptine in doses used 1.6mg/day is found to be safe and has advantages of not causing weight gain, and dyslipidemia when used in type 2 Diabetes mellitus as oral hypoglycemic drug. In our studies there was significant reduction in the Total cholesterol, LDL, TGL, No significant reduction in BMI and VLDL and No significant increase HDL were seen by the use of Bromocriptine .Further large scale studies are needed to highlight the effect of Bromocriptine on lipid profile and Body mass index in diabetic patients.

Conflicts Of Interests: Nil

Authors Funding: Nil

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