Antidepressant Activity of Phosphodiesterase 3 Inhibitor: Cilostazol

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ABSTRACT

The aim of present study was to evaluate change in depressive symptoms from baseline to 1month follow up assessment through Montgomery – Asberg depression rating scale (MADRS) in cardiovascular disease patients undergoing cilostazol therapy. Impairments in signal transduction have been implicated as possible mechanism of reduced plasticity and neuronal survival in major depressive disorders. PDE inhibitors possess a potentially powerful means to manipulate secondary messengers involved in learning, memory and mood. Cilostazol has been found to show improvement of cognitive function, prevention of cerebral ischemia, amelioration of neuronal damage and neuroprotection in animal studies. Thus PDE3 inhibitor, Cilostazol is evaluated for antidepressant activity. The study is Prospective, Single centric, open labeled, non-randomized carried out on 22 subjects fulfilling inclusion/exclusion criteria and having mild to moderate depression for at least 2 weeks prior to assessment through Montgomery Asberg Depression Rating Scale (MADRS). Subjects were selected to undergo Cilostazol (50 mg BD) therapy for 1 month duration. Follow up of the subject was carried out by MADRS after 1 month through telephonic conversation. The change from baseline to follow up score for MADRS was statistically significant. MADRS response rate at the end of one month cilostazol therapy has shown reduction in MADRS total score of > 50% relative to baseline in all 22 patients. There was complete remission rate with MADRS score of < 8 in all 22 patients at the end of treatment phase as compared to baseline. In conclusion, Cilostazol possesses antidepressant effect as evidenced through decrease in MADRS scoring as compared to baseline ratings. Thus, Cilostazol could be a drug of choice in cardiovascular patients who underwent angioplasty and on adjuvant dual antiplatelet therapy for treatment of mild to moderate depression.

Keywords: Cilostazol, PDE3 inhibitor, antidepressant activity, MADRS.

INTRODUCTION

Depression is a heterogeneous disorder that affects a person's mood, physical health and behavior. Patients with major depression have symptoms that reflect changes in brain neurotransmitter, specifically nor epinephrine (NE), serotonin and dopamine. The prevalence of major depression in the general population is estimated to suffer from depression. An estimated 5% of men and 9.5% of women experience the depressive episodes in their lifetime. Suicidal tendency remains one of the common outcomes of depression, with depressive illness being responsible for 60% of the death toll. Despite the advent of new molecule in pharmacotherapy of depression, it is unfortunate that this disorder goes undiagnosed and untreated. [1-4]

Depression is associated with an approximately two-fold increase in cardiac morbidity and mortality for various coronary heart disease (CHD) populations, including patients with recent acute myocardial infarction (AMI), patients awaiting coronary artery bypass graft (CABG) surgery, and patients post revascularization. [5] Cilostazol has been used as an antiplatelet agent and in intermittent claudication in patients with peripheral vascular disease. [6-7] Moreover, Cilostazol has antithrombotic, vasodilatory, lipid lowering, and anti proliferative effects. [8] PDE inhibitors are currently being investigated as possible memory enhancers, antidementia drugs, antidepressants and antipsychotic agents due to location of PDEs in brain at discrete sites. [9-13] Cilostazol is an alternative to milnacipran for the treatment of patients with post stroke depression as it lead to decrease in Hamilton rating scale for depression (HAM-D) after switching from milnacipran to Cilostazol (100mg/day). [14] Thus present study is designed to evaluate change in depressive symptoms from baseline to 1 month follow up assessment through Montgomery – Asberg depression rating scale (MADRS) in cardiovascular disease patients undergoing cilostazol therapy.

Study design

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The study was Prospective, Single centric, open labeled, non-randomized study involving patients with cardiovascular disease. Study protocol was approved by ethics committee of CIMS hospital, Ahmedabad with approval number I 1112.

MATERIALS AND METHODS

Screening parameters

Inclusion Criteria involved patients of both genders with age of 18 years and above. Patients with unstable angina, peripheral arterial disease, cerebrovascular stroke, and other cardiovascular disease along with condition of mild or moderate depression from at least 2 weeks as assessed through Montgomery Asberg Depression Rating Scale (MADRS) for which they have been prescribed cilostazol were included in the study.

Exclusion Criteria involved patients with high risk of bleeding, thrombocytopenia, congestive heart failure, contraindication to antiplatelet agent, and with no prior treatment with Antidepressants in past. Special population i.e. paediatrics, pregnant and lactating women were excluded from study. After screening patients were asked to give voluntary consent to participate in study through informed consent form.

The MADRS is a 10-item clinician rating of depressive symptoms. Each item is scored on a 7-point scale (0 to 6) (range 0–60). Higher scores represent higher levels of depression. The administration and scoring of the MADRS takes a trained rater approximately 10 to 20 minutes, depending upon the severity of the symptoms and difficulty of the interview. Its psychometric properties have been studied extensively in adults. [15] MADRS in adults has high interrater reliability, with estimates as high as 0.97 between a psychiatrist and general practitioner. [16] Correlation between each item and total score ranges between 0.12 (reduced appetite) and 0.84 (apparent sadness). The MADRS correlates with global ratings (0.70) and the Hamilton rating scale for depression (HRSD) (0.59). The MADRS has established scores for varying levels of symptom severity. Scores of 44, 32, 23, 15, and 7 have been suggested to designate very severe, severe, moderate, mild, and recovered depressions, respectively. [17] The scale is unidimensional and not confounded by somatic or psychomotor symptoms. [18-19] MADRS does not specify a time frame for rating the symptoms, it is usually used to assess the prior week. The MADRS generally takes about 10–15 minutes to administer to each informant.

The study was conducted for a period of two months. About 22 patients fulfilling inclusion/exclusion criteria and having depression were selected to undergo Cilostazol therapy for 1 month. Patients were considered to be depressed if they felt symptoms for at least 2 weeks before baseline assessment. Informed consent form was duly signed by patients and then they given cilostazol. Assessment was done at baseline and 1 month after cilostazol therapy (50 mg BD) for diagnosis of depression through Montgomery – Asberg depression rating scale given in table 1. Data were recorded in case record forms and converted into Excel sheets. Follow up of the patients after 1 month was carried out through telephonic conversation for MADRS ratings by clinically trained personnel.

Outcome measures

- Improvement in MADRS ratings of patients undergoing Cilostazol therapy through Montgomery-Asberg Depression Scale (MADRS) questionnaire as compared to baseline values.
- MADRS response rate: Reduction in MADRS total score of at least 50% relative to end of treatment phase as compared to baseline.
- MADRS remission rate: absolute total score of < 8 and at least 50 % reduction in MADRS total score relative to end of treatment phase. [20]

Statistical analysis

An item-total correlation (Pearson correlation) was computed for the MADRS at follow up. Effect sizes (Cohen's D) were computed for the total scale score and for each item for each measure. The within-group effect sizes were computed as the exit item (or total) score minus the baseline item (or total) score divided by the standard deviation of the change in item (or total) score. [21]

Paired t test was applied to MADRS ratings at study exit.

Table 1: MADRS interpretation

MADRS score	Impression
0-6	Normal/recovered
7-19	Mild depression
20-34	Moderate depression
35-60	Severe depression

Table 2: Baseline characteristics of the patients

S. No.	Characteristics	Number of patients (N=22)
1.	Age (yr) (mean± SD)	55.59± 8.97
2.	Male	19 (86.36%)
3.	Female	3(13.63%)
4.	Body mass index (kg/m^2) (mean± SD)	26.17±4.44
5.	Previous history & Comorbid condition	
	Hypertension	10(45.45%)
	Diabetes	6(27.27%)
	Unstable angina	5(22.73%)
	Diabetes + hypertension	2(9.09%)
	Smoking	3 (13.63 %)
	Ischemic heart disease	2(9.09%)
6.	Coronary angioplasty	22 (100%)
7.	Systolic blood pressure (mm Hg)	121.57 ± 15.83
8.	Diastolic blood pressure (mm Hg)	79.52 ± 13.93

Table 3: Concomitant medications

S. No.	Medication	Number of patients (N=22)
1.	Aspirin	22 (100%)
2.	Clopidogrel	20(90.9%)
3.	Ramipril	11 (50%)
4.	Atorvastatin	21 (95.45%)
5.	Metoprolol	12 (54.54%)
6.	Enoxaparin	17 (77.27%)
7.	Nikorandil	22 (100%)
8.	Pantoprazole	12 (54.54%)
9.	Telmisartan	6 (27.27%)

Table 4: MADRS Item Total Correlations (n=22) at Study Exit & Effect Size for Change from Baseline to Exit within the cilostazol treated group

MADRS item	Item-total correlation (Pearson correlation)	p-value	Effect size (Cohen's D)
Apparent sadness	0.01	Ns	1.7
Reported sadness	0.13	Ns	0.74
Inner tension	0.53	<0.01	1.48
Reduced sleep	0.55	<0.01	1.78
Reduced appetite	0.44	<0.05	1.31
Concentration	.043	<0.05	0.8
Lassitude	0.25	Ns	1.18
Inability to feel	0.33	Ns	1.57

Note: Cohen defines a small effect size as 0.2–0.4, a median effect size as 0.4–0.6, and a large effect size as >0.6. Ns indicate not significant

RESULTS

Total of 22 patients having mild (n=17) to moderate depression (n=5) had baseline MADRS score of 15.18±4.75 and follow up (exit score) MADRS score of 3.86±2.05. The change from baseline to follow up score for MADRS was statistically significant (p<0.0001). MADRS response rate at the end of one month cilostazol therapy has shown reduction in MADRS total score of > 50% relative to baseline in all 22 patients. There was complete remission rate with MADRS score of < 8 in all 22 patients at the end of treatment phase as compared to baseline. MADRS remission rate was achieved in 20(90.09%) patients with follow up score of < 8.

All the patients (n=22) were assigned to Cilostazol (50 mg BD) treatment for 1 month following coronary angioplasty. The clinical baseline characteristics of patients are shown in Table 2. The use of medication during the follow-up period is shown in Table 3.

Table 4 shows the exit MADRS item total correlations and effect size (Cohen's D) for change from baseline to exit within cilostazol treated group. For the MADRS, those items that showed the highest correlations with the total scores were 'inner tension' (0.53), 'reduced sleep' (0.55), 'reduced appetite' (0.44), 'concentration' (0.43) and there were no correlations with 'pessimistic thoughts' and 'suicidal thoughts' as they were not observed in any of the patients.

Effect sizes for total scores and each item on MADRS for patients treated with cilostazol (within-group effect size for change) was large for all parameters of MADRS as defined by Cohen's D.

DISCUSSION

Phosphodiesterase enzymes have been implicated to play role in learning, memory, mood, schizophrenia and depression due to their location in hippocampus. [22] Impairments in signal transduction have been implicated as possible mechanisms of reduced plasticity and neuronal survival in major depressive disorders. [23] This hypothesis provides a framework in which the pathophysiology and pharmacotherapy for depressive illness converge on cAMP-mediated signaling rather than being organized by receptor or neurotransmitter systems. [24] Elevated intracellular levels cAMP has been shown to possess antidepressant like effects. This can be achieved by PDE inhibition or by the stimulation of adrenergic receptors. [25]

The Montgomery-Asberg Depression Rating Scale (MADRS) is most commonly-used rating scale that is sensitive to treatment effects in depressed patients and assesses the range of symptoms that are most frequently observed in patients with depression. The importance of reliability of assessments in a clinical trial cannot be overestimated. [26] Thus the study was carried out with single trained interviewer to avoid interrater variability for both baseline and follow up ratings for better agreement.

The results of this study showed that cilostazol has got antidepressant effects as it leads to improvements in the depressive symptoms as evidenced by the reduction in MADRS total score at follow up. MADRS response rate was also significant in all 22 patients as it lead to reduction of >50% relative to baseline score.

It conclusion cilostazol is a drug of choice in cardiovascular patients who underwent angioplasty and on adjuvant dual antiplatelet therapy for treatment of mild to moderate depression. The antidepressant effects of cilostazol may be attributed to increased cAMP levels by inhibtion of PDE3 in hippocampus.

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