Journal of Affective Disorders 183 (2015) 149–155

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Simvastatin versus atorvastatin for improving mild to moderate depression in post-coronary artery bypass graft patients: A double-blind, placebo-controlled, randomized trial

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ARTICLE INFO

Article history:
Received 3 February 2015
Received in revised form
26 April 2015
Accepted 27 April 2015
Available online 7 May 2015

Keywords:
Atorvastatin
Coronary artery bypass
Depression
Simvastatin

ABSTRACT

Background: A decreased risk of developing depression has been reported among statin users. Aside from their lipid-lowering effects, statins are considered immunomodulatory agents and have protective effects against oxidative stress and inflammation which are well known for their association with depression. The aim of the present study was to compare the probable antidepressant effects of simvastatin and atorvastatin among post-coronary artery bypass graft (CABG) surgery patients with high and low potentials for blood-brain-barrier penetration, respectively.

Method: Forty-six outpatients who had undergone CABG in the last 6 months and suffered from mild to moderate depression participated in a parallel, double-blind, placebo-controlled trial, and were randomized to undergo 6 weeks of treatment with either simvastatin (20 mg/day) or atorvastatin (20 mg/day). Participants were evaluated using Hamilton depression rating scale (HDRS) at baseline and weeks 3 and 6. The primary outcome was to evaluate the efficacy of simvastatin in improving the depressive symptoms.

Result: General linear model repeated measures demonstrated significant effect for time × treatment interaction on the HDRS scores [F (1.62, 71.06)=3.41, P=0.048]. There was no significant difference between the treatment groups regarding the adverse events. No one experienced serious adverse event.

Limitation: The limitations of the present study were its small sample size and the short-term follow-up period.

Conclusion: Treatment with simvastatin seems to be well tolerated with superior antidepressant effects compared to atorvastatin in post-CABG patients. Long-term outcomes of this practice and its probable influence on other psychological aspects are yet to be investigated in future studies.

Trial registration: Iranian registry of clinical trials (http://www.irct.ir): IRCT201410271556N68.

1. Introduction

Numerous studies reported a higher prevalence of depression among patients with coronary artery disease (CAD) compared to the normal population (Lichtman et al., 2008). It has been estimated that between 15% and 20% of patients hospitalized due to myocardial infarction (MI) suffer from major depressive disorder (MDD) (Bush et al., 2005; Carney and Freedland, 2003) with another 20% affected by minor depression (Schleifer et al., 1989). Most importantly, MDD itself, as well as presence of depressive symptoms, is believed to be associated with poorer outcome of CAD and higher risk of developing further cardiac events (Frasure-Smith and Lesperance, 2005). The results of a meta-analysis of 29 studies which included a total number of 16,899 MI patients with an average follow-up period of 16 months demonstrated that post-MI depression is associated with a two-fold rate of mortality (Meijer et al., 2011). Moreover, in patients undergoing coronary artery bypass graft (CABG) surgery, MDD in all its minor,

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http://dx.doi.org/10.1016/j.jad.2015.04.049
0165-0327/

moderate and major forms, was reported as an independent risk factor for mortality after being adjusted for potential confounding factors (Blumenthal et al., 2003).

Even though various antidepressant agents are available for MDD, its management remains a challenge since these medications are only effective in less than half of cases (Trivedi, 2009). Furthermore, the lag in onset of antidepressant effects of the currently available treatments is known to be associated with a significant increase in morbidity and risk of suicide (Maany, 2004; Machado-Vieira et al., 2008). Thus, finding new rapid-onset therapeutic strategies could improve depression outcome.

Statins are a group of lipid-lowering agents which act via inhibition of 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase. Statins have been proven to be beneficial in both primary and secondary prevention of CAD even among individuals with cholesterol levels within normal ranges. The beneficial roles of statins have also been reported in some neuropsychiatric disorders such as dementia and Alzheimer's disease (Parsaik et al., 2014). Recent studies have reported a protective role for statins against depression, anxiety, and hostility thus suggesting positive effects of these agents on the psychological well-being (Young-Xu et al., 2003). In a recent meta-analysis of 7 observational studies with a total number of 9187 patients, use of statins was associated with a 32% decrease in risk of developing depression (Parsaik et al., 2014). The protective effect of statins against depression may be explained by several theories. Even though some older studies reported a probable association between low cholesterol levels and an increased risk of depression, the results of the most recent studies have suggested that depression may be associated with high cholesterol level as well as abnormal lipid profile (van Reedt Dortland et al., 2010; Weidner et al., 2009). Moreover, statins are also considered as immunomodulatory agents and have protective effects against oxidative stress and inflammation which are well known for their association with depression (Mulhaupt et al., 2003). Beyond these effects of statins, these agents may directly influence the brain neurons by modulating some important components of the central nervous system such as brain-derived neurotrophic factor (BDNF) and N-methyl-D-aspartate (NMDA) glutamate receptors which are assumed to be involved in the pathophysiology of depression (Castren and Rantamaki, 2010; Wood et al., 2010).

Among different statins currently available, simvastatin is known to possess the greatest ability to infiltrate the blood-brain-barrier (BBB) (Vuletic et al., 2006). In one study, the estimated potency of simvastatin in penetrating the BBB was six to seven times greater than atorvastatin, the most common statin used in management of CAD patients (Sierra et al., 2011). Moreover, the authors concluded that simvastatin is the best available choice of statin for neuroprotection against Alzheimer's disease due to its ability to access the brain and to reduce cholesterol levels as well as cell death in brain neurons (Sierra et al., 2011).

Considering the currently available data, simvastatin seems to have superior neuroprotective effects compared to atorvastatin due to its higher potency in passing the BBB. We hypothesized that the antidepressant effects of simvastatin may be equivalent or even superior to atorvastatin. Therefore, the present randomized, double-blind, placebo-controlled trial was designed to compare the probable antidepressant effects of simvastatin and atorvastatin in decreasing depressive symptoms among post-CABG patients as two different types of statins with high and low potentials for BBB penetration, respectively.

2. Patients and methods

2.1. Trial design and setting

A six-week, randomized, double-blind, placebo-controlled, parallel-group study was conducted in the Psychiatric Clinic of Tehran Heart Center, one of the largest referral heart centers in the region affiliated with Tehran University of Medical Sciences (TUMS), from November 2014 to January 2015. The study protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Science (Grant no: 19164) and was performed in agreement with the Declaration of Helsinki and its subsequent revisions. The trial was registered at the Iranian registry of clinical trials prior to conducting the study (http://www.irct.ir; registration number: IRCT201410271556N68). Written informed consent was obtained from all study participants. Participants were informed they are free to withdraw from the trial at any time without affecting their relationship with their clinical treatment.

2.2. Participants

Eligible patients were individuals 18–50 years of age with a history of CABG in the last 6 months who met the DSM IV-TR criteria for diagnosis of MDD. The inclusion criteria were confined to patients with mild to moderate depression and a Hamilton Depression Rating Scale-17 items (HDRS) score of ≤ 19.

Exclusion criteria were as follow: participants with any diagnosis other than MDD on the DSM-IV-TR axis I or II, being on any psychotropic medications or presence of any psychotic features, receiving any antidepressant medication in the last month, receiving electroconvulsive therapy (ECT) during the last two months, serum low-density lipoprotein (LDL) level of < 80, history of hypothyroidism, hepatic diseases, alcohol or substance (with the exception of nicotine) dependence, receiving any statins or any other lipid-lowering agent during the last 2 months, hypersensitivity to statins, presence of any serious medical condition or neurological problem, high levels of liver aminotransferases, pregnancy and lactation.

2.3. Interventions

Eligible participants randomly received either one tablet of simvastatin (Shahre Darou Co, Tehran, Iran; 20 mg tablets) once daily or one atorvastatin tablet (Shahre Darou Co, Tehran, Iran; 20 mg tablets) in the same manner for 6 weeks. Patients were not allowed to undergo any behavioral intervention therapy or use other lipid-lowering agent or antidepressant drugs during the study course.

2.4. Outcomes

All patients were evaluated using HDRS at baseline, weeks 3 and 6. HDRS contains 17 items (on a three-point or five-point scale) which assesses the severity of depressive-related symptoms (Hamilton, 1960). HDRS has been widely used in several clinical trials in Iran to assess the treatment efficacy and severity of depressive symptoms (Abbasi et al., 2012; Khajavi et al., 2012; Modabbernia et al., 2012; Shahmansouri et al., 2014; Zeinoddini et al., 2015). The primary outcome measure of this study was evaluation of simvastatin efficacy in improvement of depressive symptoms (HDRS Score) compared to placebo using general linear model repeated measure. Two groups were also compared with respect to reduction in HDRS score from baseline, response to treatment ($\geq 50\%$ reduction in the HRDS score) and the time needed to respond to treatment. Regarding the adverse events, a check list was provided to systemically record the adverse events during the trial course. Furthermore, all participants were asked an open-ended question about occurrence of any adverse event which was not mentioned in the checklist.