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Research report

A randomized, double-blind, clinical trial comparing the efficacy and safety of *Crocus sativus L.* with fluoxetine for improving mild to moderate depression in post percutaneous coronary intervention patients

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ABSTRACT

Objective: A significant correlation exists between coronary artery diseases and depression. The aim of this trial was to compare the efficacy and safety of saffron versus fluoxetine in improving depressive symptoms of patients who were suffering from depression after performing percutaneous coronary intervention (PCI).

Methods: In this randomized double-blind parallel-group study, 40 patients with a diagnosis of mild to moderate depression who had undergone PCI in the last six months were randomized to receive either fluoexetine (40 mg/day) or saffron (30 mg/day) capsule for six weeks. Participants were evaluated by Hamilton depression rating scale (HDRS) at weeks 3 and 6 and the adverse events were systemically recorded.

Results: By the study endpoint, no significant difference was detected between two groups in reduction of HDRS scores ($P=0.62$). Remission and response rates were not significantly different as well ($P=1.00$ and $P=0.67$; respectively). There was no significant difference between two groups in the frequency of adverse events during this trial.

Limitations: Relatively small sample size and short observational period were the major limitations of this study.

Conclusion: Short-term therapy with saffron capsules showed the same antidepressant efficacy compared with fluoxetine in patients with a prior history of PCI who were suffering from depression.

1. Introduction

There is a significant correlation between coronary artery disease (CAD) and depression. Up to 50% of patients with CAD experience some depressive symptoms during the course of their illness and among them 20% can be labeled as having a diagnosis of major depressive disorder (MDD) (Carney and Freedland, 2008). Beyond negative impact of depression on patients' quality of life, its poor prognostic consequences raise serious concerns in patients suffering from cardiovascular disorders (Stafford et al., 2007). As far as prognosis is concerned, patients with CAD and depression carry a two-fold risk of long-term mortality (Barefoot et al., 1996). Moreover, depression results in slower return to normal life, less adherence to cardiac rehabilitation and higher incidence of recurrent angina (Meijer et al., 2011; Swardfager et al., 2011). Not surprisingly, such a relationship has been confirmed between depression and all variants of CAD including unstable angina (Lesperance et al., 2000), chronic stable angina (Jespersen et al., 2013), and myocardial infarction (MI) (Fielding, 1991). Among management strategies of CAD, percutaneous coronary intervention (PCI) is one of the most well-tolerated and widely

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used options indicated for the majority of patients. Interestingly, it has been suggested that patients who undergo PCI may experience more depressive symptoms compared with other modalities of treatment (Park et al., 2012).

While reviewing the literature on depression treatment options for patients with CAD, we face inconsistencies. Although some studies support the benefits of antidepressant use in patients with coexistent CAD and MDD, recent trials could not prove long-term advantages for such medications in decreasing patients mortality rates (Berkman et al., 2003; Taylor et al., 2005). However, the value of antidepressant therapies in improving the overall patients' quality of life should not be completely discounted. In addition to failing to improve the overall mortality, there are some other issues of concern with antidepressant medications regarding their side effects in this high-risk subset of patients. Serious and life-threatening cardiac adverse events, such as blood pressure changes and arrhythmia, have been reported with tricyclic antidepressants (TCA) use which considerably limits their application in patients with CAD (Roos, 1983). While some researches indicate beneficial effects for serotonin-norepinephrine reuptake inhibitors (SNRIs), according to the current reviews, selective serotonin reuptake inhibitors (SSRIs) are the most reassuring antidepressant medications in terms of efficacy and safety in patients with cardiovascular diseases (Alvarez and Pickworth, 2003; Mavrides and Nemeroff, 2013; Pizzi et al., 2011). SSRIs are assumed to be relatively safe drugs in regards to the cardiovascular system, but even this category of antidepressants may lead to some cardiovascular side effects such as mild bradycardia, hypotension, minimal electrocardiographic changes, and bleeding (Alvarez and Pickworth, 2003; Bigger and Glassman, 2010). Another concern is drug interactions between SSRIs and some commonly used cardiac medications like clopidogrel and aspirin (Andrade, 2012). Given these facts along with other side effects seen with SSRI use such as nausea, sexual dysfunction, weight gain, and sleep disturbances, cardiologists are very reluctant to add an antidepressant medication to the mixture of cardiac patients' drug regimen.

Acceptable efficacy and a more favorable safety profile make herbal compounds novel promising entities for improving depression in patients with cardiovascular diseases (Yeh et al., 2006). Saffron is the dried stigma of a plant named *Crocus sativus L.* and has been known as the world's most expensive spice. Traditionally, this medicinal plant was used to treat a wide spectrum of diseases and its therapeutic effects on different disorders have been proven in numerous animal and human studies (Hosseinzadeh and Nassiri-Asl, 2013; Schmidt et al., 2007; Srivastava et al., 2010). Interestingly, both antidepressant and cardioprotective properties of saffron have attracted greater attention in recent years. It has been demonstrated that saffron constituents (mainly crocin) promote cardiovascular health through their antioxidant, radical scavenging, hypolipidemic, and hypotensive properties (Imenshahidi et al., 2010; Mehdizadeh et al., 2013; Montoro et al., 2012; Serrano-Diaz et al., 2012; Sheng et al., 2006). Saffron has been also shown to attenuate atherosclerosis (He et al., 2005), myocardial injury (Sachdeva et al., 2012), cardiotoxcity (Goyal et al., 2010) and development of insulin resistance (Shirali et al., 2013). Apart from its favorable effects on the cardiovascular system, saffron and its constituents are known as potent modulators of complex mental processes such as memory and mood. Several lines of evidence support memory-enhancing properties of saffron in clinical and preclinical settings (Akhondzadeh et al., 2010a, 2010b; Papandreou et al., 2011; Pitsikas et al., 2007; Wang et al., 2010). Similarly, saffron constituents have been shown to exert antidepressant activity in experimental models of depression (Wang et al., 2010). Interestingly, five separate randomized clinical trials indicate that hydro-alcoholic extract and stigma of *C. sativus L.* can significantly improve depressive symptoms in patients with MDD. In clinical studies, saffron-treated patients have experienced significantly greater improvement in depressive symptoms compared with those who received placebo (Akhondzadeh et al., 2005; Moshiri et al., 2006). Even more appealing, short-term administration of saffron preparations has been shown to be as efficient as some conventional antidepressant medications including fluoxetine (Akhondzadeh Basti et al., 2007; Noorbala et al., 2005) and imipramine (Akhondzadeh et al., 2004). These outcomes are particularly striking with regard to saffron's greater tolerability and more favorable safety profile (Modaghegh et al., 2008). Considering the special concerns around treating depression in patients with CAD, especially those who have undergone PCI, we hypothesized that saffron intake would be of benefit in these patients in order to alleviate their disabling depressive symptoms. Therefore, we conducted a randomized double-blinded clinical trial to compare the efficacy and safety of saffron capsules versus a commonly used antidepressant medication (fluoxetine) in patients who were suffering from MDD after performing PCI.

2. Methods and materials

2.1. Trial design

This was a 6-week, parallel-group, double-blind, randomized clinical trial in patients suffering from MDD who had previously undergone PCI. The trial protocol was approved by the institutional review board (IRB) of Tehran University of Medical Sciences and performed in accordance with the Declaration of Helsinki and its subsequent revisions. Written informed consent was obtained from eligible participants before their entry. Patients were informed of their right to withdraw from the project at any time without any negative effect on their relationship with health care providers. This trial was registered at the Iranian Clinical Trials Registry (IRCT201202281556N36; www.irct.ir).

2.2. Participants

Inclusion criteria. Both male and female outpatients aged 20 to 65 years were eligible to participate if they had a history of PCI in the last 6 months and met the DSM IV-TR criteria for diagnosis of MDD. We confined our inclusion criteria to mild to moderate depression and the Hamilton depression rating scale (HDRS) (Hamilton, 1960) score of 14–22. Since this was the first trial of saffron in such group of patients, we could not enroll individuals with severe depression from the ethical point of view. Patients were included only if they were suffering from significant depressive symptoms forcing them to seek treatment.

Exclusion criteria. We excluded patients with diagnosis of any other psychiatric disorder on the DSM-IV axis I or II based on a structured diagnostic interview and those who were receiving any other psychotropic medications. Patients at high risk for suicide (score ≥ 2 on the suicide item of HDRS) were referred to a psychiatrist and were not enrolled in this study. Patients were also excluded if they had received psychotropic agents, alternative medicine, or psychotherapy within 4 weeks or electroconvulsive therapy (ECT) within 8 weeks prior to entry. Other exclusion criteria were substance abuse or dependence (other than nicotine) within 3 months, serious or life-threatening illness, thyroid disease, hepatic or renal dysfunction, hypersensitivity to fluoxetine or herbal compounds, pregnancy, lactation, and oral contraception use. Women in child-bearing ages were excluded if they were willing to get pregnant.

In addition to complete physical examination performed by an expert cardiologist, laboratory tests were conducted before enrollment including complete blood count, serum electrolytes, fasting blood glucose, lipid profile, blood urea nitrogen, creatinine, and