Can *Valeriana officinalis* root extract prevent early postoperative cognitive dysfunction after CABG surgery? A randomized, double-blind, placebo-controlled trial

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Abstract

**Rationale** We hypothesized that valerian root might prevent cognitive dysfunction in coronary artery bypass graft (CABG) surgery patients through stimulating serotonin receptors and anti-inflammatory activity.

**Objectives** The aim of this study was to evaluate the effect of *Valeriana officinalis* root extract on prevention of early postoperative cognitive dysfunction after on-pump CABG surgery.

**Methods** In a randomized, double-blind, placebo-controlled trial, 61 patients, aged between 30 and 70 years, scheduled for elective CABG surgery using cardiopulmonary bypass (CPB), were recruited into the study. Patients were randomly divided into two groups who received either one valerian capsule containing 530 mg of valerian root extract (1,060 mg/daily) or placebo capsule each 12 h for 8 weeks, respectively. For all patients, cognitive brain function was evaluated before the surgery and at 10-day and 2-month follow-up by Mini Mental State Examination (MMSE) test.

**Results** Mean MMSE score decreased from 27.03±2.02 in the preoperative period to 26.52±1.82 at the 10th day and then increased to 27.45±1.36 at the 60th day in the valerian group. Conversely, its variation was reduced significantly after 60 days in the placebo group, 27.37±1.87 at the baseline to 24±1.91 at the 10th day, and consequently slightly increased to 24.83±1.66 at the 60th day. Valerian prophylaxis reduced odds of cognitive dysfunction compared to placebo group (OR=0.108, 95 % CI 0.022–0.545).

**Conclusion** We concluded that, based on this study, the cognitive state of patients in the valerian group was better than that in the placebo group after CABG; therefore, it seems that the use of *V. officinalis* root extract may prevent early postoperative cognitive dysfunction after on-pump CABG surgery.

**Keywords** Valeriana officinalis · Cognition disorder · Coronary artery bypass grafting

Introduction

Coronary artery bypass graft (CABG) surgery is one of the most commonly performed surgical procedures worldwide (Farhoudi et al. 2010). Since the introduction of cardiopulmonary bypass (CPB) in the early 1950s, the neurological consequence of cardiac surgery has been an important issue (Arrowsmith et al. 2000). Cognitive dysfunction is the most
common complication after cardiac surgery with the approximate reported incidence of 20–80% (Kilo et al. 2001). This complication is associated with increased mortality (Spiegel et al. 2011), longer hospital stay (Slater et al. 2009), increased hospital costs (Plaschke et al. 2010), reduced patient recovery (Slater et al. 2009), increased risk of dementia (Petersen et al. 2001), and long-period care (Bilotta et al. 2011).

Cognitive dysfunction presume to be the result of physiological disturbances caused by the CPB (Farhoudi et al. 2010; Van Houten et al. 2012). Brain damage caused by acute inflammation and decreased serotonin neurotransmitter are the causative mechanisms of cognitive dysfunction in patients undergoing on-pump cardiac surgery (Baumgartner 2007; Figueroa-Ramos et al. 2009). This condition has led to the development of pharmacological neuroprotective strategies in these patients (Gilmore and Wolfe 2013). Pharmacologic prophylactic treatment (e.g., cholinesterase inhibitors and antipsychotics) has been suggested as a means to prevent cognitive dysfunction in selected patients and high-risk settings (e.g., older patients, postoperation, and after stroke) (Gilmore and Wolfe 2013; Oldenbeuving et al. 2008). A meta-analysis stated that prophylactic, low-dose, and short-term administration of haloperidol or risperidone may modestly decrease delirium incidence—but not duration—in high-incidence samples who require intensive care unit (ICU) support (Gilmore and Wolfe 2013). Some other studies have not demonstrated a decrease in the incidence of cognitive dysfunction in patients receiving pharmacologic prophylactic (such as haloperidol, donepezil (Sampson et al. 2007), citicoline (Becq et al. 2009), and rivastigmine) (Gamberini et al. 2009; Kalisvaart et al. 2005; Pisani et al. 2010).

Valerian root, an herbal product consisting of the root of Valeriana officinalis L., is widely available on the market as a traditional medicine (Taibi et al. 2009). The root of V. officinalis have been used in the treatment of sleep disorders, anxiety, myalgia, and epilepsy (Bent et al. 2006; Sudati et al. 2013). Many studies have shown the anti-inflammatory properties (Jacobo-Herrera et al. 2006; Patočka and Jaki 2010), stimulatory effects on serotonin (5-HT) and acetylcholine (ACH) receptors (Dietz et al. 2005; Patočka and Jaki 2010), and reduction of sleep disturbance properties of valerian (Bent et al. 2006).

Considering that several studies showed the role of inflammation (Gorelick 2010; Peng et al. 2013), sleep disruption (Inouye et al. 1999; Sveinsson 1975), and decrease in the ACh and 5-HT neurotransmitters (Figueroa-Ramos et al. 2009) in occurrence of postoperative cognitive dysfunction, we hypothesized that valerian probably can decrease the incidence of cognitive dysfunction through stimulating ACh and 5-HT receptors (Dietz et al. 2005; Patočka and Jaki 2010) and anti-inflammatory properties (Jacobo-Herrera et al. 2006; Patočka and Jaki 2010), with reduction of sleep disturbance (Bent et al. 2006). Currently, two studies confirmed effects of valerian root on cognitive dysfunction improvement in mice (Nam et al. 2013; Wang et al. 2014). According to the safety, accessibility, and inexpensiveness of V. officinalis (Bent et al. 2006; Gooneratne 2008) and to test this hypothesis and also due to the lack of clinical evidence regarding the effect of valerian on cognitive dysfunction after cardiac surgery, this study was conducted for the first time with aim to investigate the effect of valerian root extract on the prevention of postoperative cognitive dysfunction in patients undergoing CABG surgery.

Materials and methods

Participants

After approval of the study in the Ethics Committee of the Islamic Azad University, and obtaining written informed consent from the patients, 61 adult patients of both sexes, aged 30–70 years, who are candidates for elective CABG surgery using CPB, were enrolled in this study. Exclusion criteria included the following: CABG surgery with no CPB, concomitance with other cardiac surgeries (e.g., valve replacement), reoperation, history of cerebrovascular disease, alcoholism, known mental illness, use of psychotherapeutic drugs in the last 3 months, hepatic failure (SGPT and SGOT more than 75 IU/L), severe pulmonary insufficiency, acute renal failure (creatinine ≥2 mg/dL), previous heart surgeries, heart failure (ejection fraction less than 30%), deafness, blindness, inability to speak, and sensitivity to valerian. Also, patients with pH less than 7.25 or serum base excess (BE) of less than −6 mmol/L and coagulopathy (prolonged PT, a PTT, or both) were excluded from the study.

Study design

A randomized, double-blinded, placebo-controlled trial was conducted in the Cardiothoracic Surgery and ICU units at Mazandaran Heart Center, a university teaching hospital affiliated to Mazandaran University of Medical Sciences. The trial protocol was registered at the Iranian Clinical Trials Registry (IRCT201311104190N2; www.irct.ir) and performed in accordance with the Declaration of Helsinki and its subsequent revisions. Patients were informed of their right to withdraw from the trial at any time. The study was performed between March and September 2013.

Valerian root extract

Valerian (V. officinalis, Valerianaceae) is a resistant perennial flowering plant, with heads of pink or white flowers. The roots of species belonging to the genus Valeriana are used in traditional medicine of many cultures. This genus consists of over 250 species with many more subspecies. V. officinalis L. is the official species used in Europe and Asia. Valerian, in
pharmacology and herbal medicine, is the name of supplement prepared from roots of the plant. Extract of the root is often sold in the form of capsules (Circosta et al. 2007). In this study, valerian capsules made in Goldaru Company, Isfahan, Iran, were used. Each capsule contains 530 mg dried root of *V. officinalis* (IRC; 1228022753).

**Intervention**

History taking and physical examination on the patients were conducted by an anesthesiologist, who was blinded to the study, a day before the surgery. Patients who fulfilled the inclusion criteria were randomly allocated into two groups of experimental (taking valerian) and control (taking placebo) by a nurse who was unaware of the study groups, according to numbers generated by the computer-generated list. The experimental group received valerian capsules containing 530 mg *V. officinalis* root extract, every 12 h. The placebo group, however, received placebo capsule every 12 h. The preparation of placebo capsules is as that of the valerian capsules manufactured by Goldaru Company, Isfahan, Iran. First, the contents of valerian capsules were removed, and then the capsules were filled with fixed amount of wheat flour for all randomized patients who received placebo. Hence, placebo capsules were identical to valerian capsules in shape, size, texture, color, taste, and odor. Intake of the valerian and placebo began 1 day before the surgery and continued 60 days after the surgery. Valerian or placebo was administered orally 3 h after extubation.

**Anesthesia and operation conditions**

All patients were premedicated with promethazine, midazolam, and morphine, 30–60 min before surgery by an anesthesiologist who was blinded to the study. Anesthesia in all patients was based on moderate doses of fentanyl (20 to 30 μg/kg) and midazolam (0.05 to 0.15 mg/kg), supplemented with isoflurane (<1 %) or propofol (2.5 to 4.0 mg/kg/h) during CPB. The CPB circuit included a roller pump (Stockert Instruments, Munich, Germany), a hollow-fiber membrane oxygenator (Medtronic Inc., Minneapolis, MN, USA), and a 34-μm screen arterial filter (Medtronic Inc.).

**Neurocognitive test**

The Mini Mental State Examination (MMSE) (standardized mental status interview) for screening of cognitive dysfunction was used in this study (Rudolph et al. 2006). Validity and reliability of the Persian version of the MMSE score (Folstein test) is confirmed, and it is used widely in research studies to evaluate cognitive function in several studies (Farhoudi et al. 2010; Ghafari et al. 2012). The five areas of the test were as follows: orientation (10 scores), registration (3 scores), attention and calculation (5 scores), recall (3 scores), and language and praxis (9 scores), with a maximum score of 30 points. Any score greater than or equal to 25 points is efficiently normal. The scores lower than this can indicate severe (<9 scores), moderate (10–20 scores), or mild (21–24 scores) cognitive dysfunction (Ghafari et al. 2012; Mungas 1991). The neurocognitive tests were administered three times: once the day before, at 10 days, and 2 months after the surgery (Ghafari et al. 2012). Assessments were completed by an experienced psychometrician who was blinded to the treatment group assignments. The time of the neurocognitive test and assessment was also the same (in the morning) for all patients.

**Statistical analysis**

We used the Shapiro-Wilk test to test whether data were normally distributed. Descriptive baseline characteristic comparisons for the two groups (valerian and placebo) were tabulated as median (inter-quartile range) or as percentages. Comparisons between the two groups for categorical data were statistically analyzed using chi-square or Fisher’s exact test, and for continuous data, the Mann–Whitney U test was used. The primary efficacy data on MMSE were examined using intention-to-treat analysis. General linear model (GLM) scores of MMSE between two groups were compared by repeated measurement ANOVA test. Time of evaluation was considered as the within-subject factor, and intervention state (valerian and placebo) as the between-subject factor. The group time (interaction term) was considered as group differences (between valerian and placebo groups) in their response over time. We tested Mauchley’s sphericity test for compound symmetry assumption. Additionally, we used a generalized estimating equation (GEE) model to estimate the differences in values of MMSE state (binary variable) at each time point between the two groups and also the trend of treatment after treatment. A *p* value of 0.05 or less was considered statistically significant, and a *p* value of less than 0.1 was considered marginally statistically significant. Data were analyzed using IBM SPSS statistics version 16 and STATA version 10.

**Results**

**Participants**

A total of 86 patients who were referred for CABG surgery to our hospital were screened during the study period. Of these, three patients did not meet the inclusion criteria and seven patients declined to participate in the study. From 76 patients
who were allocated in the two groups, 7 and 8 patients were lost to follow-up during the study period in case and control group, respectively. In total, 61 patients completed the present study and data from all these patients were analyzed (Fig. 1).

Basic demographic and clinical characteristics of patients in the two groups are presented in Table 1.

Results show that differences of lowest NPT during CPB, lowest pO₂ during operation (mm Hg), and duration of operation between groups are significant ($p<0.05$), but were not significant in the other factors ($p>0.05$).

Outcomes

**MMSE score and cognitive dysfunction**

Table 2 shows the mean and SD values of the preoperation and postoperation MMSE parameters of each group. As shown in Table 2, there is a marginal statistically significant time trend (within-subject differences or time effect) for recall domain of MMSE ($p<0.1$), and there is no statistically significant time trend for overall MMSE and other domains ($p>0.05$). There is statistically significant differences in the values of MMSE and all domains except language and praxis between groups (between-subject differences or group effect) ($p<0.1$). The following were identified that contrary to the MMSE and all domain trends in the intervention group was stable, the placebo group showed a statistically significant downward trend (group time interaction or interaction effect) ($p<0.05$) except for attention and calculation domain of MMSE where this difference was not statistically significant (no interaction effect) ($p>0.1$).

After adjusting of other variables, GEE model revealed that valerian prophylaxis reduced odds of cognitive dysfunction compare to placebo group (estimate: $-2.22$, OR $=0.108$, 95% CI $0.022-0.545$).

**Discussion**

Cognitive dysfunction and neuroinflammation are associated with cardiac surgery after CPB (Scott et al. 2014; Van Harten et al. 2012). We evaluated the effectiveness of valerian root extract on the prevention of postoperative cognitive dysfunction in patients undergoing CABG surgery. The major finding of this study was that the patients who received valerian had significantly lower incidence of the cognitive dysfunction as well as greater improvement in their cognitive function during the 8 weeks after CABG surgery compared to the other group that received placebo. Any score greater than or equal to 25 points (out of 30) is normal. The scores lower than this indicate cognitive dysfunction. MMSE score had relatively a stable or rising trend after 2 months in patients receiving valerian, but it is considerably reduced in the placebo group at the end of study.

To the best of our knowledge, there are no clinical trials which evaluate preventive effects of valerian root on cognitive dysfunctions in vivo. Recently, the results of the two studies showed that *V. officinalis* could improve cognition dysfunction in vitro (Nam et al. 2013; Wang et al. 2014).

Wang et al. suggest that valerian could protect the brain neurons and ameliorate amyloid-beta-induced cognitive dysfunction by enhancing the cerebral cholinergic function, hence
Table 1 Basic demographic and clinical characteristics of patients in both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valerian group</th>
<th>Placebo group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 (62-68)</td>
<td>66 (63.7-69)</td>
<td>0.54</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>17/14</td>
<td>19/11</td>
<td>0.34</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.2 (28.3-33.1)</td>
<td>30.3 (28.5-33.1)</td>
<td>0.58</td>
</tr>
<tr>
<td>Literate</td>
<td>13 (41.9 %)</td>
<td>13 (43.3 %)</td>
<td>0.91</td>
</tr>
<tr>
<td>Smoker</td>
<td>6 (19.4 %)</td>
<td>4 (13.3 %)</td>
<td>0.73</td>
</tr>
<tr>
<td>HTN</td>
<td>30 (96.8 %)</td>
<td>28 (93.3 %)</td>
<td>0.61*</td>
</tr>
<tr>
<td>COPD</td>
<td>6 (19.4 %)</td>
<td>3 (10 %)</td>
<td>0.47*</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>1 (3.2 %)</td>
<td>1 (3.3 %)</td>
<td>&gt;0.99*</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>45 (40-50)</td>
<td>45 (40-46.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Preoperative hospital stay (days)</td>
<td>2 (2-3)</td>
<td>2 (2-2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Postoperative hospital stay (days)</td>
<td>5 (5-5)</td>
<td>5 (4-5.25)</td>
<td>0.83</td>
</tr>
<tr>
<td>ICU stay (day)</td>
<td>2 (2-3)</td>
<td>2 (2-2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Duration of operation (h)</td>
<td>3 (3-4)</td>
<td>3.77 (3.35-4.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of MV in ICU (h)</td>
<td>6 (6-8)</td>
<td>6.73 (5.7-8)</td>
<td>0.49</td>
</tr>
<tr>
<td>Duration of intubation in ICU (h)</td>
<td>7 (6-8)</td>
<td>6.38 (5.83-8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Duration of CPB (min)</td>
<td>60 (54-62)</td>
<td>60 (53.7-65.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>Duration of aortic cross-clamping (min)</td>
<td>38 (32-48)</td>
<td>40 (35-45)</td>
<td>0.74</td>
</tr>
<tr>
<td>Lowest NPT during CPB (°C)</td>
<td>30 (29-31)</td>
<td>29 (29-30)</td>
<td>0.02</td>
</tr>
<tr>
<td>Lowest HB during CPB (g/dL)</td>
<td>6 (6-7)</td>
<td>6 (6-7)</td>
<td>0.29</td>
</tr>
<tr>
<td>Lowest MAP during CPB (mmHg)</td>
<td>60 (50-60)</td>
<td>58.5 (55-65)</td>
<td>0.31</td>
</tr>
<tr>
<td>Lowest SpO₂ during operation (%)</td>
<td>98 (98-99)</td>
<td>97 (97-99)</td>
<td>0.15</td>
</tr>
<tr>
<td>Lowest pO₂ during operation (mmHg)</td>
<td>179 (170-192)</td>
<td>166.0 (159-180)</td>
<td>0.01</td>
</tr>
<tr>
<td>Blood transfusion during operation</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Patients receiving prolong inotrope (&gt;12 h)</td>
<td>1 (3.2 %)</td>
<td>2 (6.7 %)</td>
<td>0.61*</td>
</tr>
<tr>
<td>Patients requiring IABP</td>
<td>4 (12.9 %)</td>
<td>1 (3.3 %)</td>
<td>0.35*</td>
</tr>
<tr>
<td>Postoperative dysrhythmia</td>
<td>AF</td>
<td>8 (25.8 %)</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>VT</td>
<td>2 (6.5 %)</td>
<td>0.67*</td>
</tr>
<tr>
<td></td>
<td>VF</td>
<td>1 (3.2 %)</td>
<td>0.29*</td>
</tr>
</tbody>
</table>

Data are expressed as the median (inter-quartile range) or as number (percentages). 
BMI body mass index, HTN hypertension, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, MV mechanical ventilation, ICU intensive care unit, CPB cardiopulmonary bypass, NPT nasopharyngeal temperature, HB hemoglobin, MAP mean arterial pressure, SpO₂ saturation of peripheral oxygen, pO₂ partial pressure of oxygen, IABP intra-aortic balloon pump, AF atrial fibrillation, VT ventricular tachycardia, s ventricular fibrillation.

* Fisher’s exact test.

Increasing the secretion of ACh and enhancing the choline acetyltransferase (ChAT) activity (Wang et al. 2014). Nam et al. investigated the effects of extract from valerian root in adult and aged mice. Study results indicate that valerian root extract (100 mg/kg) and valeric acid enhance cognitive function, promote cell proliferation and neuroblast differentiation, and decrease serum corticosterone and lipid peroxidation in aged mice (Nam et al. 2013).

Inflammation may be an important mechanism causing cognitive dysfunction (Gorelick 2010). Peng et al., in a meta-analysis, provided evidence that cognitive dysfunction is indeed associated with the concentrations of peripheral inflammatory markers, especially interleukin-6 and S-100B (Peng et al. 2013).

Considering that acute inflammation and decreased serotonin neurotransmitter resulting from abnormal tryptophan metabolism are the two mechanisms of developing cognitive dysfunction in these patients (Baumgartner 2007; Figueras-Ramos et al. 2009), likely, valeric acid contained in valerian through stimulating serotonin receptors and inhibiting of inflammatory factor NF-κB (Jacobo-Herrera et al. 2006; Patočka and Jakl 2010) result in decrease the incidence of cognitive dysfunction in patients, and this led us to assume that the prophylactic effect shown by valerian on cognitive
dysfunction is most likely to result from anti-inflammatory actions and neuroprotective effects (Baumgartner 2007; Figueroa-Ramos et al. 2009; Wang et al. 2014). Although, more research is still needed in this regard.

Sleep disruption is another potential risk factor for cognitive dysfunction in cardiac surgical patients (Sveinsson 1975). The relationship between sleep deprivation and cognitive dysfunction has been studied in a many studies (Fulda and Schulz 2001; Yildizeli et al. 2005).

The available evidence indicates that valerian root might improve sleep quality without producing side effects (Bent et al. 2006; Taavoni et al. 2011). *V. officinalis* is effective in reducing insomnia associated with oxidative stress (Sudati et al. 2009).

Therefore, other possible explanations for the effectiveness of valerian root extract in reducing postoperative cognitive dysfunction in our study may be that valerian through improvement of sleep quality leads to a reduction in cognitive dysfunction.

The result of our study showed that the cognitive state of patients in the valerian group was better than in the placebo group at the 10 days after CABG; therefore, it seems that the use of *V. officinalis* root extract can prevent early postoperative cognitive dysfunction after on-pump CABG surgery. Moreover, since valerian has anticoronaryspastic, antihypertensive, and antiinfl ammatory (Circosta et al. 2007; Murti et al. 2011) properties, its application is reinforced in patients undergoing heart surgery.

This study, however, has some limitations. One limitation of the present study was that we only evaluate the patients’ cognitive function in the morning and did not evaluate it at the evening. Also, we only used MMSE as a subjective measurement of cognitive function and did not utilize several different screenings for diagnosis of cognitive dysfunctions, which indicates the need for further research. In addition, the study was not large enough to completely prove a benefit from valerian for cognitive dysfunction prophylaxis after CABG. In conclusion, the present study provides evidence for *V. officinalis* root extract as a prophylactic strategy in the prevention of cognitive dysfunction after CABG surgery. However, further robust randomized, blinded studies with large sample sizes are required in this field.

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