Can *Glycyrrhiza glabra* L. Reduce Delirium after Coronary Artery Bypass Graft Surgery?

Abolfazl Firouzian Hadi Darvishi Khezri

Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

Keywords

Glycyrrhiza glabra L. · Cognitive brain function ·
Coronary artery bypass grafting

Schlüsselwörter

Glycyrrhiza glabra L. · Hirnleistung ·
Koronararterien-Bypass-Chirurgie

Coronary artery bypass graft (CABG) surgery is one of the most commonly performed invasive procedures worldwide [1, 2]. Since the introduction of cardiopulmonary bypass (CPB), the neurological consequence of CABG surgery has been an important subject [2]. Delirium is a major problem after CABG surgery with the approximate reported incidence rate of 20–80% [2]. This complication is associated with increased mortality, longer hospital stay, increased hospital costs, and long-term care [2–4]. Regarding the high incidence of delirium in patients undergoing CABG surgery, prophylactic treatment is preferable. Hence, pharmacological neuroprotective strategies have been developed for these patients [3, 4]. A meta-analysis indicated that preoperative low-dose and short-term administration of haloperidol or risperidone may modestly reduce delirium occurrence in high-risk patients that need intensive care unit (ICU) [4]. Other clinical trials have not reported any decreases in the incidence rate of delirium in patients receiving pharmacologic prophylactic (haloperidol, donepezil [5], citicoline [6], and rivastigmine) [7–9].

Acute inflammation and reduced serotonin neurotransmitter are the most important causes of delirium in these patients [10, 11]. In a meta-analysis, Peng et al. [12] showed the role of peripheral inflammatory markers, such as interleukin-6 and S-100 β , in postoperative delirium [13]. Although some studies indicated that use of compounds with brain protective activities (such as propofol, aprotinin and lidocaine) can prevent delirium after CABG surgery, no sufficient evidence was presented to make a change in standard clinical practice.

Licorice (*G. glabra*, species: Leguminosae) is a worldwide popular herbal medicine. Just 3 out of the numerous species of licorice are usually used as commercial drugs, including *G. glabra*, *Glycyrrhiza echinata* L., and *Glycyrrhiza uralensis* Fisch. In traditional medicine, the roots and rhizomes (underground stems) of licorice are currently used as therapeutic compounds in many Asian and European countries. Licorice mainly consists of a mixture of glycyrrhizinic acid, glycyrrhizic acid, glycyrrhizin, isoflavones, isoliquiritigenin, hispaglabridin B, paratocarpin B, and glabridin. Furthermore, this plant has been used as antidote and demulcent, expectorant, antioxidant, antiulcer, laxative, antipyretic, antimicrobial, and anti-inflammation agent [14]. Glabridin, a major active flavonoid in licorice, has anti-atherosclerotic, anti-inflammatory, anti-nephritis, radical scavenging activities and antidepressant-like effects [15]. Moreover, this compound has been reported to be useful for renovascular and cardiovascular diseases [16]. Ojha et al. [16] evaluated the cardioprotective effect of licorice against ischemia-reperfusion injury induced by ligation of left anterior descending coronary artery in rats. Their results confirmed the cardioprotective activity of licorice by alleviating oxidative stress in myocardial ischemia-reperfusion injury [16].

Safe brain-protective agents, such as licorice, could be utilized to reduce the neuroinflammation and delirium caused by CPB in these patients. Muralidharan et al. [14] investigated the cerebroprotective effect of 250 and 500 mg/kg of licorice roots in hypoxic rats and indicated that licorice has a cerebro-

protective effect. This effect may be mediated by its antioxidant activities. Results of this in-vitro study showed that the licorice extract administration could significantly reverse the decreased levels of glutamate and dopamine and reduced acetylcholinesterase (AChE) activity. Moreover, antioxidant enzyme levels (superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase) were restored close to normal range [14].

In-vitro and in-vivo analyses demonstrated that glabridin has neuroprotective effects by enhancing the survival of neurons and preventing their death and apoptosis [15]. Glabridin is a type of isoflavonoid (isoflavane) derived from the extract of licorice root. Yu et al. [15] showed that 25mg/kg (higher dose) of glabridin significantly decrease the focal infarct volume, cerebral histological damage, and apoptosis induced by middle cerebral artery occlusion in rats. Glabridin was purchased from the National Institute for the Control of Pharmaceutical and Biological Products (NICBP) (purity 99.0%). It was dissolved in dimethyl sulfoxide (DMSO), and freshly prepared for this study. That study presented primary evidence that glabridin exhibits neuroprotective effects via inhibition of oxidative stress. These findings indicate that glabridin had neuroprotective effects by modulation of multiple pathways associated with apoptosis.

Although the majority of potent antioxidants demonstrate suitable efficacy in animal studies, there are only few studies showing the therapeutic effects of this extract on humans. Thus, further studies are warranted to further investigate the biochemical mechanisms underlying the protective effect of glabridin on brain and to collect evidence for clinical use of licorice in delirium management.

In conclusion, licorice could theoretically be used as a single supplement or in combination with other drugs to decrease delirium after cardiac surgery with CPB. Although licorice and its major constituent glabridin have positive therapeutic effects on human health, there are only few clinical trials that investigate the ability of these compounds on cerebral protection, clinical efficacy, and the mechanism responsible for their pharmacological activities. Further research addressing the preventive role of licorice and glabridin on delirium after cardiac surgery with CPB is recommended.

Disclosure Statement

The authors declare that they have no conflict of interest concerning this manuscript.

References

- Farhodi M, Mehrvar K, Afrasiabi A, et al.: Neurocognitive impairment after off-pump and on-pump coronary artery bypass graft surgery: an Iranian experience. *Neuropsychiatr Dis Treat* 2010;6: 775–778.
- Arrowsmith JE, Grocott HP, Reves JG, Newman MF: Central nervous system complications of cardiac surgery. *Br J Anaesth* 2000;84:378–393.
- Merino JG, Latour LL, Tso A, et al.: Blood-brain barrier disruption after cardiac surgery. *AJNR Am J Neuroradiol* 2013;34:518–523.
- Gilmore ML, Wolfe DJ: Antipsychotic prophylaxis in surgical patients modestly decreases delirium incidence – but not duration – in high-incidence samples: a meta-analysis. *Gen Hosp Psychiatry* 2013; 35:370–375.
- Sampson EL, Raven PR, Ndhlovu PN, et al.: A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. *Int Journal Geriatr Psychiatry* 2007;22:343–349.
- Campbell N, Boustani MA, Ayub A, et al.: Pharmacological management of delirium in hospitalized adult: a systematic evidence review. *J Gen Intern Med* 2009;24:848–853.
- Kalisvaart KJ, De Jonghe JFM, Bogaards MJ, et al.: Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc* 2005;53:1658–1666.
- Gamberini M, Bolliger D, Buse GAL, et al.: Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery – a randomized controlled trial. *Crit Care Med* 2009;37:1762–1768.
- Pisani MA, Murphy TE, Araujo KLB, Van Ness PH: Factors associated with persistent delirium after intensive care unit admission in an older medical patient population. *J Critical Care* 2010;25: 540:e1–e7.
- Figueroa-Ramos MI, Arroyo-Novoa CM, Lee KA, Padilla G, Puntillo KA: Sleep and delirium in ICU patients: a review of mechanisms and manifestations. *Intensive Care Med* 2009;35:781–795.
- Baumgartner WA: Neurocognitive changes after coronary bypass surgery. *Circulation* 2007;116: 1879–1881.
- Peng L, Xu L, Ouyang W: Role of peripheral inflammatory markers in postoperative delirium (POCD): a meta-analysis. *PloS One* 2013;8:e79624.
- Gorelick PB: Role of inflammation in cognitive impairment: results of observational epidemiological studies and clinical trials. *Ann N Y Acad Sci* 2010; 1207:155–162.
- Muralidharan P, Balamurugan G, Babu V: Cerebroprotective effect of *Glycyrrhiza glabra* Linn. root extract. *Bangladesh J Pharmacol* 2008;4:60–64.
- Yu X-Q, Xue CC, Zhou Z-W, et al.: In vitro and in vivo neuroprotective effect and mechanisms of glabridin, a major active isoflavan from *Glycyrrhiza glabra* (G. glabra). *Life Sci* 2008;82:68–78.
- Ojha S, Golechha M, Kumari S, Bhatia J, Arya DS: *Glycyrrhiza glabra* protects from myocardial ischemia-reperfusion injury by improving hemodynamic, biochemical, histopathological and ventricular function. *Exp Toxicol Pathol* 2013;65:219–227.