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Effects of *Ginkgo biloba* extract on cerebral oxygen and glucose metabolism in elderly patients with pre-existing cerebral ischemia☆

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KEYWORDS
Ginkgo biloba extract;
Brain;
Glucose;
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Summary
Specific aim: Cerebral injury caused by hypoperfusion during the perioperative period is one of the main causes of disability and death in patients after major surgery. No effective protective or preventative strategies have been identified. This study was designed to evaluate the effects of *Ginkgo biloba* extract on cerebral oxygen and glucose metabolism in elderly patients with known, pre-existing cerebral ischemia.
Methods: Sixty ASA (American Society of Anesthesiologists) II—III patients, diagnosed with vertebral artery ischemia by transcranial Doppler ultrasonography (TCD), and scheduled for elective total hip replacement surgery, were enrolled in the study. They were randomly allocated to receive either 1 mg/kg *Ginkgo biloba* extract (G group $n = 30$) or normal saline (D group $n = 30$) after induction of anesthesia. Blood samples were collected from radial artery and jugular venous bulb catheters for blood gas analysis and determination of glucose and lactate concentrations preoperatively, before surgical incision, at the end of surgery, and on post-op day 1. Arterial O_2 content (CaO_2), jugular venous O_2 content ($CjvO_2$), arteriovenous O_2 content difference ($Da\text{-}jvO_2$), cerebral oxygen extraction rate (CEO_2), and arteriovenous glucose and lactate content differences (Da-jvGlu and Da-jvLac) were calculated.
Results: There were no significant differences in CaO_2 or Da-jvGlu during surgery between groups ($p > 0.05$). However, the Ginkgo group had higher $CjvO_2$, internal jugular venous oxygen saturation ($SjvO_2$) and lower CEO_2, $Da\text{-}jvO_2$ and Da-jvLac at the end of surgery (T2) and on post-op day 1 (T3) than those in the control group ($p < 0.05$).

☆ The trial was registered at the Chinese Clinical Trial Registry (ChiCTR) (www.chictr.org), registration number ChiCTR-TRC-14004380.

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Conclusion: *Ginkgo biloba* extract can improve cerebral oxygen supply, decrease cerebral oxygen extraction rate and consumption, and help maintain the balance between cerebral oxygen supply and consumption. It has no effect, however, on cerebral glucose metabolism in elderly patients with known, pre-existing cerebral ischemia.

Introduction

Brain tissue hypoperfusion, which may occur during the perioperative period, can decrease cerebral oxygen supply. *At risk* patients may be prone to brain injury because cerebral tissue is very sensitive to hypoxia. Moreover, brain injury is an important factor affecting a patient's prognosis after surgery. Prevention of perioperative cerebral injury has become an important research topic in the field of anesthesia. Attempts to protect the brain from these insults have included administering medications (including anesthetics) and measures, such as hypothermia, prior to a cerebral ischemic event. It has been confirmed that effective brain protection can significantly prolong the tolerance time of an ischemic brain event, decreasing the incidence and degree of central neuronal damage.[1]

Ginkgo biloba extract (EGb761) injection contains *Ginkgo biloba* extract 17.5 mg (24% ginkgo flavone glycoside, 3.1% ginkgo lactone, 2.9% ginkgo lactone).[2] *Ginkgo biloba* extract[1] has been shown to possess polyvalent properties, including anti-oxidation, anti-apoptosis and anti-inflammation that have been reported to be the main mechanisms of neuroprotection.[3] A large number of animal experiments have confirmed that *Ginkgo biloba* extract, acting as a free radical scavenger, can protect neuronal cell membranes and suppress free radical induced apoptosis. *Ginkgo biloba* extract appears to have a neuroprotective effect in patients with neurodegenerative diseases.[4,5] Deng et al.[6] found that Ginaton improves cerebral oxygen supply and promotes superoxide dismutase (SOD) activity (inhibiting free radical production) in patients undergoing hypothermic cardiopulmonary bypass (CPB). It is unclear whether *Ginkgo biloba* extract has perioperative neuroprotective effect in elderly patients at risk for cerebral ischemia. This study was conducted to examine the effects of *Ginkgo biloba* extract on cerebral oxygen and glucose metabolism in elderly patients with known cerebral ischemia and determine its feasibility of use in clinical practice.

Methods

This was a prospective, randomized, double-blind trial. Approval was obtained from the Local Research Ethics Committee and written informed consent was obtained from each patient. The study was conducted from 2014/04/01 to 2014/06/30. Sixty ASA (American Society of Anesthesiologists) II—III patients aged greater than 60 years scheduled for elective total hip replacement surgery participated in the study. Preoperatively, they were diagnosed with vertebrobasilar artery insufficiency by transcranial Doppler ultrasonography (TCD). Diagnostic criteria was according to the guidelines of the American Institute of Ultrasound in Medicine (AIUM).[7] Patients with diabetes mellitus, cardiovascular or other cerebrovascular disease, hyperlipidemia, osteoarthritis, neurological or psychiatric disease, abnormal renal or hepatic function, taking multiple drug medications for other diseases, and any known sensitivity to study medications were excluded. Patients who were hearing or vision impaired, illiterate, with mental retardation, previous sedative or antidepressant use or with a history of alcoholism or past anesthesia were also excluded. Patients received no anesthetic premedication. Patients were allocated randomly (by computer-generated random numbers) to receive either an infusion of *Ginkgo biloba* extract injection (Shineway Pharmaceutical Co, Hebei, China) or placebo. Study drugs (*Ginkgo biloba* extract and placebo) were prepared by the hospital pharmacy in identical containers marked with the name of the project, the investigator's name, and consecutive numbers. Patients and investigators were blinded to the infusion.

Following placement of an intravenous (IV) line, all patients received atropine 0.01 mg/kg IV. Subsequently, induction of anesthesia was performed in all patients with midazolam 0.04 mg/kg, propofol 1—2 mg/kg, and remifentanil 0.5 μg/kg. Cisatracurium 0.15 mg/kg was administered to facilitate endotracheal intubation and intermittent positive pressure ventilation. Anesthesia was maintained with an infusion of remifentanil 0.2 μg/kg/min and inhalation of sevoflurane (1—2% end-tidal concentration) with oxygen. Depth of anesthesia was maintained by adjusting the concentration of sevoflurane to achieve a Bispectral Index Score of 40—60. Heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), $P_{ET}CO_2$ (end-tidal carbon dioxide partial pressure) and hemoglobin oxygen saturation (SpO_2) were recorded every 5 min. Muscle relaxant reversal medications were not administered at the end of the surgery. The endotracheal tube was removed when patients were breathing spontaneously and awake and met all other extubation criteria. After inducing anesthesia, *Ginkgo biloba* extract injection[8] 20 ml diluted in normal saline to a volume of 250 mL (group G) or 250 mL of normal saline (group D) was administered by intravenous infusion over 30 min before surgical incision. No intravenous analgesics were administered postoperatively. The incidence of adverse events including allergic reactions, gastrointestinal discomfort, nausea and vomiting, headache, lower blood pressure and postoperative complications such as myocardial infarction, cerebral infarction, cerebral hemorrhage and arrhythmia were recorded.

Blood samples were collected from radial artery and jugular venous bulb catheters for blood gas analysis by ABL 700 blood-gas analyzer (Radiometer Co, Denmark) and determination of arterial oxyhemoglobin saturation (SaO_2), internal jugular venous oxygen saturation ($SjvO_2$), arterial blood oxygen partial pressure (PaO_2), arterial blood carbon dioxide partial pressure ($PaCO_2$), internal jugular venous blood oxygen partial pressure ($PjvO_2$), hemoglobin (Hb),