Serum glial cell line–derived neurotrophic factor levels and postoperative cognitive dysfunction after surgery for rheumatic heart disease

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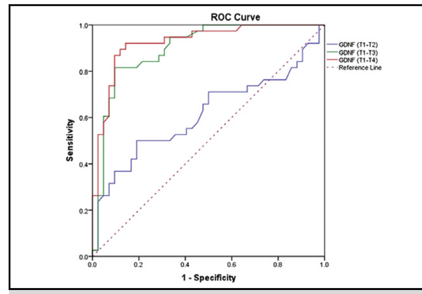
ABSTRACT

Objective: Postoperative cognitive dysfunction is an important complication of cardiac surgery with poor outcomes. Serum glial cell line–derived neurotrophic factor levels are decreased in patients with Alzheimer's disease, but the association between glial cell line–derived neurotrophic factor levels and postoperative cognitive dysfunction is poorly understood. The present study aimed to investigate the prognostic value of postoperative serum glial cell line–derived neurotrophic factor levels to predict postoperative cognitive dysfunction in patients with rheumatic heart disease undergoing heart valve replacement.

Methods: This was a prospective observational study of 80 patients undergoing elective heart valve replacement surgery from June 2015 to June 2016 at the Affiliated Hospital of Southeast Medical University. Cognitive functions were assessed 1 day before and 7 days after surgery. Serum glial cell line–derived neurotrophic factor levels were measured by an enzyme-linked immunosorbent assay before (T1) and 1 (T2), 2 (T3), and 7 (T4) days after surgery. Perioperative parameters were evaluated to assess the relationship between glial cell line–derived neurotrophic factors and postoperative cognitive dysfunction.

Results: Postoperative cognitive dysfunction was identified in 38 patients (47.5%) 7 days after surgery. Average glial cell line–derived neurotrophic factor levels at 2 and 7 days after surgery in the postoperative cognitive dysfunction group were lower than in the nonpostoperative cognitive dysfunction group at the same time points ($P < .001$). ⊿Glial cell line–derived neurotrophic factor (T1-T3) and ⊿glial cell line–derived neurotrophic factor (T1-T4) were identified as good predictors of postoperative cognitive dysfunction with threshold for postoperative cognitive dysfunction detection of 49.10 and 60.90, respectively.

Conclusions: The perioperative glial cell line–derived neurotrophic factor levels in patients with postoperative cognitive dysfunction were lower than in patients without postoperative cognitive dysfunction. Glial cell line–derived neurotrophic factor could be an effective predictor for the occurrence of postoperative cognitive dysfunction. The results reveal a potentially important role of decreased glial cell line–derived neurotrophic factor levels in postoperative cognitive dysfunction, with possible treatment targets. (J Thorac Cardiovasc Surg 2017;■:1-8)



Receiver operating characteristic analysis of the average ⊿GDNF at T2, T3, and T4 compared with T1.

Central Message

Perioperative GDNF levels could be an effective predictor for the occurrence of POCD.

Perspective

Although POCD is a common complication after cardiac surgery, the pathophysiology of POCD is poorly understood. Intraoperative GDNF levels of patients with POCD are lower than in patients without POCD. Perioperative GDNF levels are effective predictors of POCD in patients undergoing cardiac surgery. The results provide a new insight into the diagnosis and possible treatment targets for POCD.

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Abbreviations and Acronyms

ACT	= activated clotting time
AS	= Alzheimer's disease
CSF	= cerebrospinal fluid
GDNF	= glial cell line–derived neurotrophic factor
MMSE	= Mini-Mental State Examination
POCD	= postoperative cognitive dysfunction

Scanning this QR code will take you to supplemental figure, table, and video for this article.

Rheumatic heart disease is a serious condition that often requires surgical valve replacement.[1] These surgeries may involve extracorporeal circulation, depending on the exact procedure selected by the surgeons.[1] Although surgical techniques and brain-protection strategies have been improved, postoperative cognitive dysfunction (POCD) is a common complication after cardiac surgery and extracorporeal circulation,[2-5] especially among patients with rheumatic heart disease.[6,7] The occurrence of POCD has been associated with multiple adverse outcomes, including longer hospital stay,[8] increased mortality,[9] and decreased long-term quality of life.[10] Currently, it is not possible to classify a patient with POCD using standard classification criteria, such as the International Statistical Classification of Disease 9th Revision or the Diagnostic and Statistical Manual of Mental Disorders IV. Nevertheless, POCD is typically defined as a significant and persistent change in mental status as assessed by poorer than expected performance on postoperative neurocognitive tests.[11]

Determining the causes of POCD is important to identify strategies for its prevention. Despite a number of studies, the pathophysiology of POCD remains poorly understood. Descriptive studies have identified older age and lower education levels as being associated with an increased risk of POCD,[12] but these factors also predict cognitive decline in population studies without surgery.[13] POCD is defined as a significant dysfunction in cognitive performance and likely has a pathogenesis similar to that of Alzheimer's disease (AD).[14]

Glial cell line–derived neurotrophic factor (GDNF) is a protein that promotes the survival of many types of neurons.[15] GDNF levels are low in patients with AD.[8,16] Decreased serum GDNF levels in patients with AD could be related to altered brain function.[17] Therefore, GDNF could be a marker for POCD in patients undergoing cardiac surgery.

Therefore, the present study aimed to evaluate the relationship between postoperative serum GDNF levels and POCD and to investigate the ability of postoperative serum GDNF levels to predict POCD in patients undergoing heart valve replacement surgery (Video 1).

PATIENTS AND METHODS

Patients

This was a prospective observational study of patients with rheumatic heart disease undergoing elective heart valve replacement between June 2015 and June 2016 at the Affiliated Hospital of Southeast Medical University, China. The inclusion criteria were (1) 20 to 70 years of age; (2) confirmed rheumatic heart disease; and (3) indications for heart valve replacement. The exclusion criteria were (1) Mini-Mental State Examination (MMSE) score less than 24 before surgery; (2) history of psychiatric or neurological disorders, cardiothoracic surgery, or any severe visual or auditory disorders; (3) refusal to participate or cannot speak or understand Chinese language; (4) delirious state; or (5) missing biomarker measurements. The study protocol was approved by the Affiliated Hospital of Southwest Medical University Ethics Committee (KY2016003). The study was registered at the Chinese Clinical Trial Registry (ChiCTR-IPD-15006534). A written informed consent was obtained from the patients or their relatives before study enrollment.

Clinical Assessment

On admission, demographic factors such as age, gender, education, body mass index, and the American Society of Anesthesiologists status were recorded. Chronic smoking was defined as smoking more than 20 cigarettes per day for 1 month. Alcoholism was defined as consumption of an equivalent of 150 mL of alcohol per week. The New York Heart Association classification was determined by a cardiologist. The possible perioperative confounding factors, such as the duration of on-pump time, duration of aorta crossclamping, duration of recovery temperature, duration of surgery, and amount of transfused blood, were recorded.

Anesthesia

The routine vital signs of the patients were monitored, and the patient received oxygen inhalation (6 L/min). Anesthesia induction included intravenous injection of penehyclidine hydrochloride 0.01 mg/kg, midazolam 0.03 to 0.05 mg/kg, fentanyl 8 to 10 μg/kg, vecuronium 0.15 mg/kg, and etomidate 2 to 3 mg/kg. After anesthesia induction and tracheal intubation, the patient underwent catheterization of the left radial artery and right internal jugular vein. Invasive arterial blood pressure and central vein pressure were continually monitored. Anesthesia maintenance included intravenous pump of midazolam (0.01-0.015 mg/kg/min), vecuronium (0.06-0.08 mg/kg/min), and fentanyl (8-10 μg/kg/min). Generally, the doses of the drugs was maintained according to the patient's body weight, but the dose of narcotic drug was adjusted according to the patient's conditions during surgery, such as the amount of blood loss, the volume of extracorporeal circulation perfusion, and the changes in vital signs of patients. The doses of the drugs were usually progressively decreased during surgery, and the doses were increased as the patient's body temperature and metabolism increased. Occasionally, to adjust the depth of anesthesia, a single dose of midazolam, fentanyl, vecuronium, and etomidate could be added (0.03-0.05 mg/kg, 8-10 μg/kg, 0.15 mg/kg, and 2-3 mg/kg, respectively). Vasoactive drugs (eg, dopamine, dobutamine, sodium nitroprusside, and epinephrine) were pumped through a central venous catheter according to the intraoperative conditions and surgical procedure.

Cardiopulmonary Bypass

The priming solution was lactated Ringer's solution and polygeline injection; the ratio of crystalloid osmotic pressure/colloid osmotic pressure