Mechanism Study of PK2 Pathway Improving Neurometabolic Coupling Dysfunction to Alleviate Perioperative Neurocognitive Disorders

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Research Period: June 2026 – March 2027

Study Protocol

Protocol Summary
Study Design: Cohort study
Study Type: Established cohort study
Total Cases: 40 cases

Risk / Benefit Analysis
To explore the biological predictive factors of perioperative neurocognitive disorders, provide strong theoretical support for subsequent clinical treatment, improve patients' prognosis and reduce related adverse risks.

Risk Judgment: No greater than minimal risk
Minimal risk means the possibility and degree of expected risks in the study are not greater than those in daily life, routine physical examination or psychological tests.

Study Duration: June 01, 2026 to March 31, 2027

1. Research Background

Perioperative neurocognitive disorders (PND) derives from postoperative cognitive dysfunction (POCD) and has been renamed as PND according to the latest international consensus in recent years. PND refers to changes in mental state, social interaction and cognitive ability after surgery. Severe cases may be accompanied by personality changes and decreased social behavioral ability.

As a severe complication of the central nervous system (CNS), the occurrence of PND is related to surgical factors. Advanced age is recognized as an important risk factor for the development of PND, which has become a major challenge for the growing aging population.

More and more studies have confirmed that neuroinflammation plays an important role in the pathogenesis of PND, and glial cell activation is critical to central nervous system dysfunction. Genomic analysis of activated astrocytes shows that similar to macrophages, activated astrocytes can be divided into pro-inflammatory and neurotoxic A1 phenotype, as well as anti-inflammatory and reparative A2 phenotype.

Studies on chronic neurodegenerative diseases such as ALS and Parkinson's disease have shown that A1 astrocytes exert adverse effects on neurons and promote disease progression. It is speculated that surgery induces A1 activation of astrocytes, resulting in abnormal energy metabolism of astrocytes, insufficient energy supply to neurons, neuronal damage, and ultimately the occurrence of PND.

Preliminary experimental results showed that astrocytes are predominantly A1 activated in mouse PND models, and their energy metabolism disorder may lead to abnormal metabolic coupling between astrocytes and neurons.

Prokineticin-2 (PK2) is a chemokine-like signaling protein. It binds to G-protein coupled receptors PKR1 and PKR2 to regulate multiple physiological functions including angiogenesis, reproduction and innate immunity. Moreover, PK2 plays important roles in circadian rhythm, energy metabolism and neuroprotection.

Recent studies have shown that exogenous PK2 exerts protective effects on motor dysfunction, dopamine depletion and dopaminergic neuron degeneration in neurodegenerative disease models. In vitro astrocyte culture, PK2 can induce astrocyte proliferation and intracellular calcium mobilization. Further studies indicate that PK2 affects astrocyte migration, alters mitochondrial energy metabolism, reduces pro-inflammatory factors, and upregulates antioxidant proteins such as Arginase-1 and Nrf2.

Overexpression of PK2 in primary astrocytes induces A2 phenotypic transformation, upregulates A2 marker expression, and enhances glutamate uptake capacity of astrocytes. Previous studies have confirmed that Nrf2 agonist Resolvin D1 improves astrocyte energy metabolism, enhances metabolic coupling and supporting effects on neurons, and alleviates cognitive dysfunction in TBI models.

Our preliminary experiments found that PK2 expression is decreased in the hippocampus of PND model mice. Exogenous PK2 intervention significantly improved astrocyte phenotype, neuronal energy metabolism and cognitive function in mice. Therefore, PK2-mediated transformation of astrocytes into A2 phenotype and improvement of neuron-glia metabolic coupling may be a potential therapeutic strategy for PND.

However, the correlation of PK2 level with the incidence and severity of cognitive impairment in clinical PND patients has not been reported. This study intends to analyze the expression trend of PK2 in elderly patients undergoing hip replacement surgery in Nanjing First Hospital. Combined with postoperative neuropsychological scale evaluation, we will analyze the correlation between PND incidence and peripheral PK2 level, and further confirm the internal relationship between PK2 and PND pathogenesis.

2. Research Objectives

This study aims to explore the pathogenesis and potential therapeutic targets of perioperative neurocognitive disorders (PND). Neuroinflammation and astrocyte phenotypic transformation (A1 to A2 shift) play key roles in PND development. PK2 has potential functions in regulating astrocyte phenotype, improving cellular energy metabolism and neuroprotection.

The specific objectives are as follows:
To analyze the expression level and dynamic change of PK2 in elderly patients undergoing hip replacement surgery;
To combine postoperative neuropsychological evaluation to clarify the correlation between PND incidence and PK2 level;
To provide clinical evidence for PK2 as a potential biomarker and therapeutic target for PND.

3. Study Design, Methods and Procedures

3.1 Study Design

Study type: Prospective, single-center, observational cohort study
Randomization: No randomization
Study center: Department of Anesthesiology, Nanjing First Hospital

Sample size: A total of 40 patients will be enrolled, including 20 in PND group and 20 in non-PND group.

3.2 Study Methods

This is a prospective, single-center, observational cohort study. Venous blood samples will be collected at 1 day before surgery, postoperative day 1 and day 3 to detect the expression trend of PK2, oxidative stress and inflammatory indicators. Combined with neuropsychological scales, the correlation between PK2 level and PND incidence will be analyzed. No clinical intervention will be performed on routine diagnosis and treatment.

3.3 Study Procedures

3.3.1 Subject selection

Elderly patients aged 65–80 years undergoing elective hip replacement surgery in Nanjing First Hospital will be enrolled. Informed consent will be obtained before enrollment.

3.3.2 Perioperative management

All patients received routine preoperative fasting. Venous access and invasive arterial pressure monitoring were established. MAP, HR, RR, SpO2, body temperature and BIS were monitored. General anesthesia was induced with etomidate 2mg/kg, cis-atracurium 0.2mg/kg and sufentanil 0.4ug/kg. After tracheal intubation, mechanical ventilation was performed. Anesthesia was maintained with propofol and remifentanil infusion, with BIS maintained at 40–60. Blood pressure and heart rate fluctuation were controlled within 20% of baseline. Postoperative analgesia pump was applied after stable vital signs.

3.3.3 Neuropsychological assessment

MMSE, Geriatric Depression Scale and MoCA (Beijing version) were performed 1 day before surgery to evaluate baseline cognitive function. According to postoperative cognitive outcomes, patients were divided into PND group and non-PND group. Postoperative MMSE, CAM and MoCA were assessed at postoperative day 1 and day 3.

3.3.4 Laboratory detection

Peripheral venous blood (3ml) was collected at preoperative day 1, postoperative day 1 and day 3 for detection of PK2, oxidative stress indicators (SOD, GSH, CAT) and inflammatory factors (TNF-α, IL-1β). Correlation analysis between PK2 level and PND occurrence was performed.

4. Eligibility Criteria

4.1 Inclusion Criteria

- Age between 65 and 80 years old
- ASA physical status class Ⅰ – Ⅲ

- Elective hip replacement surgery

4.2 Exclusion Criteria
- MMSE score ≤ 24
- Severe cardiopulmonary, hepatic or renal dysfunction
- Recent use of sedatives or antidepressants, long-term alcohol abuse
- History of severe mental diseases including depression, schizophrenia, bipolar disorder and mental retardation
- History of severe craniocerebral injury, cerebrovascular disease, hydrocephalus, intracranial tumor, Parkinson's disease, Huntington's disease, epilepsy or other neurological diseases
- Severe visual or hearing impairment
- Unable to complete cognitive assessment due to advanced age, low education level or other reasons

5. Alternative Treatment Options
This is an observational study without interfering with routine clinical diagnosis and treatment. All patients receive standard perioperative management according to hospital clinical pathways. Participation in this study will not affect patients' clinical treatment choices.

6. Detection Items and Time Points
6.1 Blood detection (preoperative day 1, postoperative day 1, postoperative day 3): PK2, SOD, GSH, CAT, TNF-α, IL-1β
6.2 Neuropsychological assessment:
Preoperative 1 day: MMSE, Geriatric Depression Scale, MoCA (Beijing version).
Postoperative day 1 and day 3: MMSE, CAM, MoCA (Beijing version)
Patients were divided into PND group and non-PND group according to cognitive assessment results.

7. Outcome Evaluation
This is an observational cohort study without clinical intervention. The main evaluation is the correlation of PK2 level with PND incidence, as well as the changes of oxidative stress and inflammatory indicators.

8. Adverse Event Observation and Management
This study is an observational cohort study and does not interfere with clinical diagnosis and treatment. All adverse events will be recorded in detail.

9. Data Safety Monitoring
A data safety monitoring plan will be formulated according to study risk. All adverse events will be recorded and reported to the Ethics Committee, competent authorities and regulatory departments in a timely manner. The

principal investigator will regularly review cumulative adverse events and organize investigator meetings for risk assessment if necessary.

10. Statistical Analysis

SPSS 26.0 and R 4.2.0 will be used for statistical analysis.
10.1 Measurement data: Normal distribution expressed as mean ± standard deviation, independent t-test for inter-group comparison; non-normal distribution expressed as median (interquartile range), Mann-Whitney U test for inter-group comparison.
10.2 Enumeration data: Expressed as case number and percentage; Chi-square test or Fisher's exact test was used for inter-group comparison.
10.3 Missing data: Multiple imputation for continuous variables; mode imputation for categorical variables.

11. Ethical Principles

This study complies with the Declaration of Helsinki and the Ethical Review Measures for Biomedical Research Involving Human Subjects of China. The study will be initiated only after approval by the Institutional Ethics Committee. Patient privacy protection, free participation, reasonable compensation, risk control, vulnerable subject protection and research-related injury compensation principles will be strictly followed.

12. Research Schedule

June 01, 2026 – December 31, 2026: Patient enrollment and data collection
January 01, 2027 – March 31, 2027: Data analysis, manuscript writing and research achievement publication

13. Research Team and Division of Work

Wang Xiaoliang: Chief Physician, Department of Anesthesiology; Project Leader, Study Design
Xu Yajie: Attending Physician, Department of Anesthesiology; Data Collection, Manuscript Writing
Zhang Wenwen: Attending Physician, Department of Anesthesiology; Data Analysis, Manuscript Revision
Hu Jing: Attending Physician, Department of Anesthesiology; Study Monitoring and Management

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