Effect of pregabalin on cerebral outcome after cardiopulmonary bypass with deep hypothermic circulatory arrest in rats

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Objective: Activation of presynaptic voltage-gated calcium channels and release of glutamate play a central role in neuronal necrosis after cardiopulmonary bypass with deep hypothermic circulatory arrest. Pregabalin binds to the $\alpha 2$-δ subunit of voltage-gated calcium channels resulting in reduced glutamate release. The aim of this study is to evaluate the effect of pregabalin on cerebral outcome after cardiopulmonary bypass with deep hypothermic circulatory arrest through an established rat model allowing long-term survival.

Methods: Male Sprague–Dawley rats were randomized to receive intraperitoneal injection of 30 mg/kg of pregabalin or an equal amount of normal saline 1 hour before cardiopulmonary bypass (n = 10, each). Rats were cooled to a pericranial temperature of 18°C and underwent deep hypothermic circulatory arrest for 60 minutes. Neurologic performance was assessed at postoperative days 3, 7, and 12. Cognitive performance (Morris water maze) was assessed daily from postoperative day 3 to 12 when histologic assessment was performed.

Results: Neurologic scores were significantly better in the pregabalin group than in the control group at all time points of measurements. Morris water maze latencies were not statistically different between the groups. The percentage of necrotic neurons in the cerebral cortex was significantly less in the pregabalin group compared with the control group (8.6% [interquartile range, 5.0-8.9] vs 13.6% [interquartile range, 6.9-18.6], $P = .045$), whereas no difference was observed in the hippocampus.

Conclusions: Preemptive treatment with pregabalin conveyed a beneficial influence on functional and histologic cerebral outcome in rats undergoing 60 minutes of deep hypothermic circulatory arrest after cardiopulmonary bypass without any noticeable side effects. (J Thorac Cardiovasc Surg 2014;148:298-303)

Cerebral injury remains a major complication after cardiac surgery, affecting patients' outcome and resource use, yet its prevention proves to be difficult.[1] Principal causes accounting for the postoperative cerebral injury after cardiopulmonary bypass (CPB) include cerebral emboli, hypoperfusion, and systemic inflammatory response.[2] On the extreme side of hypoperfusion, deep hypothermic circulatory arrest (DHCA), a technique intermittently used for the repair of complex pediatric and adult congenital cardiac and aortic arch lesions, poses a substantial risk for cerebral injury, mandating a neuroprotective strategy.[3,4]

After depletion of adenosine triphosphate (ATP) caused by ischemia, presynaptic neurons undergo ischemic discharges and activation of voltage-gated calcium channel (VGCC) occurs, resulting in excessive release of excitatory amino acids, such as glutamate. These events lead to increased calcium influx to the cell, alterations in protein kinase activities, and ultimately neuronal cell death.[5,6] Glutamate excitotoxicity persists for hours after reperfusion, which continues to trigger these complex and interrelated biochemical events leading to neuronal cell death.[7]

Pregabalin, which has been widely used to control neuropathic pain, potently binds to the $\alpha 2$-δ subunit of VGCC.[8] Its binding at this site reduces calcium influx at presynaptic nerve endings, resulting in reduced release of glutamate and noradrenalin, an action mechanism expected to protect neurons from ischemia/reperfusion injury. Indeed, pregabalin exerted anti-apoptotic and anti-inflammatory effects accompanied by improved functional outcome in a rat model of spinal cord injury.[9] It also showed promising results in a mouse model of middle cerebral artery occlusion in terms of reduction in neuronal loss.[10] Despite this theoretic background, evidence regarding pregabalin's influence on cerebral outcome in a cardiac surgical setting using CPB is lacking.

The aim of this study was to validate the influence of preemptive administration of pregabalin on functional (cognitive and neurologic) and histologic cerebral outcome

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Abbreviations and Acronyms

ATP = adenosine triphosphate
CPB = cardiopulmonary bypass
DHCA = deep hypothermic circulatory arrest
IQR = interquartile range
MAP = mean arterial pressure
NMDA = N-methyl-D-aspartate
POD = postoperative day
VGCC = voltage-gated calcium channel

using a clinically relevant rat model of CPB with 60 minutes of DHCA.[11]

METHODS

Animals and Drug Treatment

This study was approved by the Duke University Institutional Animal Care and Use Committee, and all procedures met the National Institutes of Health guidelines for animal care (Guide for the Care and Use of Laboratory Animals, available at: www.nap.edu/catalog/5140.html). Twenty male Sprague–Dawley rats (age, 14-16 weeks; weight, 400-450 g; Charles River Laboratories, Inc, Wilmington, Mass) were studied. Animals were randomly allocated to receive 2 mL of 0.9% sodium chloride solution intraperitoneally with (pregabalin group, n = 10) or without (control group, n = 10) pregabalin 30 mg/kg, after anesthetic induction at 60 minutes before the commencement of CPB. Pregabalin was graciously provided free of charge through a compound transfer program by Pfizer Inc., New York, NY.

Cardiopulmonary Bypass and Deep Hypothermic Circulatory Arrest

Fasted rats were anesthetized for 5 minutes with 5% isoflurane in oxygen in a transparent induction box. After anesthetic induction, the trachea was intubated and the lungs were mechanically ventilated with a tidal volume of 10 mL/kg and respiratory rate of 60 to 65 beats/min to maintain the arterial carbon dioxide tension between 35 and 45 mm Hg (Harvard Rodent Respirator, Harvard Apparatus, Boston, Mass). During surgery, anesthesia was maintained with 2.0% to 2.5% isoflurane and fentanyl (25 μg/kg, intravenous, as a bolus injection).

Animals were prepared for CPB as previously reported.[11] Briefly, the tail artery was cannulated for aortic inflow, a multistaged venous return cannula was placed near the junction of the inferior vena cava and right atrium through the right external jugular vein, and the right superficial caudal epigastric artery was cannulated for monitoring (model 90603A, SpaceLabs, Inc, Redmond, Wash) mean arterial pressure (MAP). After the cannulation of the tail artery and jugular vein, animals received 150 units of heparin. During CPB, anesthesia was maintained using 0.5% to 1.2% isoflurane and fentanyl (intravenous, 150 μg/kg). No paralytics were administered until just before CPB when pancuronium (0.1 mg/kg) was administered to prevent spontaneous breathing during CPB. Fentanyl and pancuronium were repeated (at half the dose) at 30-minute intervals, as necessary. Pericranial temperature was monitored with CSC 32 (OMEGA Engineering, Inc, Stamford, Conn). The CPB circuit consisted of a venous reservoir, a peristaltic pump (Tygon; Cole-Parmer Instrument, Vernon Hills, Ill), a membrane oxygenator, and an arterial inflow cannula. An in-line flow probe (2N806 flow probe and T208 volume flowmeter; Transonic Systems, Inc, Ithaca, NY) was used to continuously measure CPB flow. The bypass circuit was primed with approximately 8 mL of 6% hydroxyethyl starch 130/0.4. One hundred units of heparin were added to the prime. Arterial blood gases were analyzed using a GEM Premier 3000 blood gas/electrolytic analyzer (model 5700, Instrument Laboratories, Inc, Lexington, Mass). Basic physiologic data, including MAP, temperature, and blood gases, were collected 15 minutes before commencement of CPB, 10 minutes before DHCA, 10 minutes before weaning from CPB, and 15 minutes and 2 hours after weaning from CPB.

CPB was commenced at a flow rate of 160 to 180 mL/min/kg and then decreased during the cooling period of 30 minutes to a target pericranial temperature of 18°C. After reaching 18°C, the rats were subjected to DHCA confirmed by the presence of asystole and the absence of any measurable MAP, while carefully draining the venous blood to a reservoir. After 60 minutes of DHCA, CPB was reinstituted and the rats were warmed to a pericranial temperature of 34°C for 30 minutes while gradually increasing the flow rate to 160 to 180 mL/min/kg. Then the rats were weaned from CPB, and heparin-induced anticoagulation was allowed to dissipate spontaneously without protamine. After decannulation, rats were maintained anesthetized with 0.5% to 1.2% isoflurane, intubated, and ventilated for 2 hours while warming the rats to a pericranial temperature of 36°C to 37°C. When adequate spontaneous breathing resumed, the animals were extubated and recovered in an oxygen-enriched box for 24 hours with free access to water and food. During the first 6 hours of recovery, they were continuously observed to identify signs of immediate cerebral death and severe neurologic dysfunction (fixed pupils, absence of spontaneous breathing, seizures, and inability to ambulate). Animals demonstrating signs of severe neurologic dysfunction were killed (2 rats in the control group and 1 rat in the pregabalin group died 1 day after DHCA. These rats were replaced with new rats). All other rats were returned to their cages and housed individually. All animals were supported for 12 days postoperatively for neurologic and neurocognitive testing. On the 12th postoperative day (POD), animals were killed for histologic evaluation.

Neurologic and Neurocognitive Testing

On the 3rd, 7th, and 12th PODs, animals underwent standardized functional neurologic testing using an established neurologic scoring system that evaluates 4 different functions: general status, simple motor deficit, complex motor deficit, and sensory deficit.[12] The score given to each animal at the completion of the testing (by an observer blinded to group assignment) was the sum of all 4 individual scores: 0 was the minimum (best) score, and 48 was the maximum (worst) score.

In addition to the neurologic evaluation, neurocognitive outcome was evaluated daily (starting on the third POD) in the Morris water maze using a computerized video tracking system (EthoVision; Noldus, Wageningen, The Netherlands).[13] The Morris water maze consisted of a 1.5-m–diameter, 30-cm–deep pool of water (27°C) with a hidden submerged (3 cm below the surface) platform in 1 quadrant. Rats were placed in the water in a dimly lit room. The time to locate the submerged platform (defined as the latency) was measured to test for impairment in visuospatial learning and memory components of neurocognition. Rats underwent daily testing in the water maze with 4 trials per testing period, each limited to 90 seconds of water exposure. Each of the trials was begun from a separate quadrant. Testing was performed for 10 consecutive days until the 12th POD.

Histologic Examination

After completion of the testing on the final day (12th POD), animals were anesthetized with isoflurane and perfusion-fixed in situ by intracardiac infusion of buffered 4% paraformaldehyde solution. After brain were embedded in paraffin, they were sliced at 5 μm in thickness. Necrotic cell death was identified by acid fuchsin-celestine blue and quantified by counting necrotic neurons in 5 representative areas of the cortex and the CA1 section of the hippocampus at 40× magnification.

Statistics

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC). All data are expressed as mean ± standard deviation or median

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