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Glutamate/Aspartate Supplementation during Cardiopulmonary Bypass: Effect on Postoperative Neurocognitive Function

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ABSTRACT

In this randomized trial, we investigated the effect of glutamate/aspartate-containing cardioplegia on neurocognitive function in 70 patients undergoing first-time elective coronary artery bypass graft surgery. Half of the patients received glutamate/aspartate, and the other 35 patients served as controls and received crystalloid cardioplegia. Neurocognitive function after surgery was assessed with the Mini–Mental State Examination performed before surgery and again on postoperative day 3. Although patients in both groups scored slightly lower postoperatively (17 versus 18 of a total of 30 points), no significant group differences were found. Our results indicate that glutamate/aspartate supplementation had no impact on neurocognitive function after coronary artery bypass graft surgery.

INTRODUCTION

Despite remarkable progress in surgical, cardiopulmonary bypass (CPB), and anesthetic techniques, neurocognitive damage remains an important cause of postoperative morbidity in cardiac surgery [Hindman 1999; Weissrock 2005]. The etiology of neurocognitive damage is likely to be multifocal; including macro- and microemboli, cerebral hypoperfusion, inflammation, and nonpulsatile flow [Pugsley 1994].

Glutamate loading has been shown to protect single isolated perfused cardiomyocytes against metabolic inhibition. Although the mechanism underpinning this protection is unknown, glutamate administration during reperfusion has been shown to reduce myocardial infarct size [King 2003]. Glutamate is a key excitatory neurotransmitter in the central nervous system (CNS). In addition, glutamate has a key role during the brain development. For example, in synaptogenesis and in adult CNS, glutamate has an important role in learning and memory processes [Vizi 2000; Bach-y-Rita 2002].

Using the Mini Mental State Exam (MMSE) (Table 1) to assess patient cognitive function, we investigated the use of glutamate and aspartate as an energy substrate in a consecutive series of 100 patients undergoing CAB surgery.

PATIENTS AND METHODS

The study was conducted in accordance with the provisions of the Declaration of Helsinki (amended in 1989) and with the approval of Kocatepe University, Faculty of Medicine Ethics Review Committee.

We considered for inclusion all patients age 58 to 76 years who were referred to a single cardiothoracic surgical team for elective, primary coronary revascularization. Exclusion criteria included history of neurological (including previous transient ischemic attacks, stroke, or seizures), psychiatric, gastrointestinal, hepatic, renal, or hematologic and clotting system disorders; evidence of drug abuse (prescribed or nonprescribed) within the previous 2 years; regular use of antiepileptics or antidepressants; and conditions requiring emergency or repeat procedures.

The MMSE (Table 1) was used to measure cognitive function on the day before surgery and 3 days later. Patients were randomly assigned to either group 1, who received glutamate/aspartate, or group 2, the control group. Following randomization but before taking any study medication, patients underwent preoperative MMSE (1 day before surgery). Throughout the surgical procedure standard physiological monitoring was performed, including electrocardiogram, arterial pressure, central venous pressure, nasopharyngeal temperature, fraction of inspired oxygen (FiO_2), end-tidal CO_2 concentration, peripherial O_2 saturation, and urine output. Anesthesia was induced with 2 to 3 mg/kg propofol, 1 to 10 μg/kg fentanyl, and 0.1 mg/kg rocuronium and maintained with nitrous oxide in oxygen (FiO_2, 0.4 to 0.5) and incremental doses of rocuronium and an opiate. Pressors, inotropic agents, and antiarrhythmics were used as needed. Intraoperative blood losses were not significant. There were no instances of significant hypotension, hypertension, hypothermia, or

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Table 1. Mini–Mental State Examination

Section	Total Possible Score
Orientation	
Time: What is the (year) (season) (date) (day) (month)?	5 ☐
Place: Where are we: (country) (city) (part of city) (number of flat/house) (name of street)?	5 ☐
Registration	
Test giver names 3 objects, taking 1s to say each, then ask the patient to name all 3. Give 1 point for each correct answer. Repeat until patient learns all 3. Count trials and record.	3 ☐
Attention and calculation	
Serial counting by 7's: 1 point for each correct, stop after 5 answers. Alternatively, spell "world" backwards.	5 ☐
Recall	
Recall the 3 objects repeated above. Give 1 point for each correct.	3 ☐
Language	
Name a pencil and watch (2 points).	
Repeat "No ifs, ands, or buts" (1 point).	
Follow a 3-stage command: "Take a paper in your right hand, fold it in half, and put it on the floor'(3 points).	
Read and obey the following: Close your eyes (1 point).	
Write a sentence (1 point).	
Copy a design (1 point).	9 ☐
Total	30 ☐

systemic hypoxemia.

CPB was established with a flatbed membrane oxygenator with a cardiotomy reservoir/filter and 2 or 3 low-pressure cardiotomy suckers. Moderate hypothermia (32°C) was used during CPB. Pump flow was adjusted to achieve 2.4 L/min per m at 37°C and 1.8 L/min per m at 32°C. Mean arterial pressure was maintained between 50 and 60 mm Hg. Group 1 patients received antegrade glutamate/aspartate-enriched (15 mmol/L) crystalloid cardioplegia, and group 2 patients received antegrade crystalloid cardioplegia without glutamate/aspartate. During the postoperative course, all patients were electively ventilated for variable periods depending on several factors, at least until the morning of the day following surgery. MMSE was performed 3 days postoperatively.

Statistical Analysis

Statistical analysis was performed with SPSS 11.5 for Windows. *P* values <.05 were considered statistically significant. A *t* test was used because the patient groups had parametric and independent conditions.

RESULTS

From a consecutive series of 100 patients over a 2-year period, 70 consenting patients were randomized into 1 of 2 study groups and 30 patients were excluded on the basis of abnormal laboratory baseline values, withdrawal of consent, the discovery of a history of disallowed medication or systemic disorder, or delay or difficulty in completing preoperative assessments. The remaining 70 patients, 35 patients receiving glutamate/aspartate (group 1) and 35 controls (group 2), underwent surgery according to protocol. The 2 groups were comparable with respect to demographics and MMSE scores. Mean age, CPB duration, and the lowest temperatures during CPB did not differ significantly between the 2 groups (Table 2). Biochemical, hematologic, and clotting screen data both before and after surgery showed no differences attributable to the use of glutamate. Perioperative nasopharyngeal temperatures, pump flow rates, perioperative and postoperative blood pressures, and pulse rates showed no differences between groups. Electrocardiogram monitoring revealed that most patients remained in sinus rhythm, again with no difference between groups. MMSE scores are shown in Table 3. Mean MMSE scores did not differ significantly between the 2 groups (Figure).

Table 2. Baseline Patient Data*

	Group 1	Group 2	*P*†
Age, y	68 ± 6	69 ± 4	.790
Cardiopulmonary bypass duration, min	152 ± 45	144 ± 33	.814
Lowest temperature, °C	30 ± 4	30 ± 3	.879

*Values are mean ± SD.

†*P* > .05 indicates no statistically significant difference.

DISCUSSION

The reported incidence of clinical neuropsychiatric dysfunction after CPB varies considerably, but the rates of neurologic complications after CPB may be as high as 40% [Bronster 2006]. The etiology of cognitive dysfunction after cardiac surgery is multifactorial and includes cerebral microembolization, global cerebral hypoperfusion, systemic and cerebral inflammation, cerebral temperature perturbations, cerebral edema, and possible blood-brain barrier dysfunction, all superimposed on genetic differences in patients that may make them more susceptible to injury or less able to recover from injury once it has occurred [Browne 1999; Gladstone 2002; Lewis 2005]. We did not observe any neurologic complications in our series.

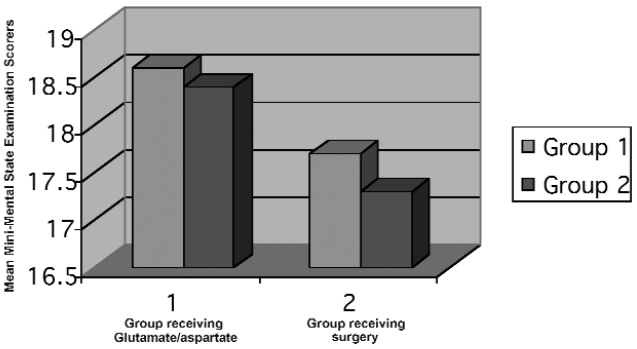
In the early 1950s experimental models of CPB showed promise, but initial human trials were disappointing. In just 50 years CPB has progressed from a risky laboratory

Table 3. Mean Mini–Mental State Examination (MMSE) Scores*

	Preoperative MMSE	Postoperative MMSE	*P*†
Group 1	18.6	17.7	.636
Group 2	18.4	17.3	.777

*Possible MMSE score 0 to 30. Postoperative MMSE administered on day 3.

†*P* > 0.05 indicates no statistically significant difference.



Scores for the Mini–Mental State Examination.

experiment to an event occurring many times daily throughout the world. Despite numerous technical advances, however, neurologic and neuropsychiatric dysfunction continues to be significant and undeniable risks of cardiac surgery [Smith 1986]. The most commonly used form of cerebral protection during CPB is hypothermia. Another approach to improving cerebral outcome during cardiac surgery is to use drugs or techniques that might protect the brain [Newman 1996; Smith 1996]. The use of membrane rather than bubble oxygenators and other changes in surgical anesthetic and perfusion practice, including the choice of filters, has already been associated with a decline in the incidence of neuropsychological sequelae. Although controversial, the administration of prophylactic thiopental infusions, which completely suppress electroencephalographic activity, immediately prior to and during intracardiac procedures has been reported to decrease the incidence and severity of neurologic deficits. Studies suggest that magnesium may also be beneficial [Bhudia 2006]. The role of calcium channel blockers (nimodipine and nicardipine) and N-methyl-D-aspartate (NMDA) antagonists (ketamine) remains largely investigational [Butterworth 2002; Nagels 2004]. Although controversial, the use of calcium channel blockers and NMDA antagonists has been reported to decrease the incidence and severity of neurologic deficits [Arrowsmith 1998] and to inhibit convulsions induced by NMDA and reduce cerebral damage in animal models of focal ischemia, properties shared with dizocilpine (MK-801). Its modest NMDA antagonism is apparently due to an active desglycinated metabolite [Ozyurt 1988]. Maximal neuroprotection occurred in the animal studies when the drug was administered before the onset of cerebral ischemia.

It is well established that glutamate has 2 opposing effects on the CNS, excitotoxicity and metabolic support. The first process appears to involve ligand-gated ionotropic glutamate receptors and the other comprises G-protein–coupled metabotropic glutamate receptors (mGluR). Evidence for neuroprotection has involved primarily agonists selective for the group I family of mGluR. Glutamate, aspartate, and nonselective mGluR agonists are neurotoxic when applied directly to cortical neurons or hippocampal slice cultures [Bruno 1995].

Glutamate/aspartate loading has been shown to protect single isolated perfused cardiomyocytes against metabolic inhibition and wash-off. The mechanism underpinning this protection is unknown. Both clinical and animal experiments have demonstrated the cardioprotective effects of the amino acid L-glutamate, but the underlying mechanisms remain unknown. Glutamate administration during reperfusion reduced myocardial infarct size by 60%, improved left ventricular function, and increased the synthesis rate and concentration of myocardial glycogen during reperfusion [King 2003].

Glutamate is important during brain development, playing a key role in synaptogenesis. In the adult CNS, glutamate is important in learning and memory processes [Smith 2000]. Large numbers and wide distribution of glutaminergic synapses in the brain make the CNS particularly vulnerable to uncontrolled release of glutamate, which may occur during ischemia and postischemia. The excitotoxic action of glutamate is considered a key player in postichemic brain damage. Despite the significant role of this neurotransmitter in the pathogenesis of ischemic brain damage (particularly in focal brain ischemia), a complex combination of metabolic events occurs during and after ischemia, and thus glutamate is not the only culprit in nervous tissue damage [Vizi 2000].

Weissrock et al [2005] suggested that the MMSE could be systematically integrated into pre- and postoperative screening. The MMSE (Table 1) is a good instrument for assessing cognitive function but takes up to 10 min to perform and cannot fit easily into a standard consultation. We used the MMSE to measure cognitive function [Burker 1995; Newman 1995, Stump 1995] to assess the effect of glutamate in further reducing the morbidity of CAB and observed that administration of glutamate/aspartate as energy substrates during cardiac surgery had no statistically significant impact on subsequent neurocognitive function.

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