



Assessing the Neurocognitive Function Effects of Ketamine in Cardiac Surgical Patients

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Abstract

Background: Despite remarkable progress in surgical, Cardio Pulmonary Bypass (CPB) and anesthetic techniques, neurocognitive damage still remains an important cause of postoperative morbidity in cardiac surgery. The aetiology of neurocognitive damage is likely to be multifocal; including macro and micro emboli, cerebral hypoperfusion, inflammation and nonpulsatile flow. N-methyl-D-aspartic Acid (NMDA) receptors play an important role during neurocognitive damage. Ketamine is a non-competitive antagonist to the phencyclidine site of NMDA receptor for glutamate and directly suppresses proinflammatory cytokine production. The aim of the present study was to evaluate whether ketamine has neuroprotective effects during open-heart surgery through the use of neurocognitive tests.

Materials and Methods: We considered all patients aged between 58-76 years who were referred to a single cardiothoracic surgical team for elective, primary coronary revascularization. Patients were excluded from the study for the following reasons: a history of neurological, psychiatric, gastrointestinal, hepatic, renal, hematologic and clotting systems disorder and repeat procedures. Patients undergoing CPB were randomized 2 groups: Group 1 (ketamine) (n=25) or Group 2 (propofol) (n=25). In the propofol group, anesthesia was induced with 3 mg/kg propofol, 1 µg/kg remifentanyl, 0.1 mg/kg vecuronium. Remifentanyl 0.5 µg/kg/min to 1 µg/kg/min was infused intravenously throughout the whole procedure. In the ketamine group, anesthesia was induced with 1 mg/kg to 2 mg/kg propofol, 1 mg to 2 mg ketamin, 0.1 mg/kg vecuronium. Ketamin 1 mg/kg/hr were infused intravenously. Pressors, inotropic agents and antiarrhythmics were used as needed. The Mini-Mental State Examination (MMSE) was administered the day before surgery and three days later. The change in scores for MMSE was calculated for each patient and the entire group. The results were compared statistically with paired simple t-test.

Results: The mean age, CBP duration, lowest temperature was not statistically significant (Table 1). Perioperative and postoperative blood pressures and pulse rates showed differences between groups. There were no preoperative differences between the groups on any of the mean MMSE score (Table 2). The ECG monitoring revealed that most patients remained in sinus rhythm, with no difference between groups.

Conclusion: We could not demonstrate that intraoperatively administered ketamine resulted in greater neuroprotective effects compared with propofol. Ketamine in combination with propofol during cardiac surgery is associated with a stable hemodynamic profile. Propofol may reduce the delivery of micro emboli to the cerebral circulation by decreasing the cerebral blood flow. Propofol has a direct neuroprotective effect *in vitro*, although Roach et al. could not demonstrate a protective effect of propofol during open-heart surgery. Propofol enhances the anti inflammatory response to surgery by several mechanisms. This might have masked a neuroprotective effect of ketamine because propofol was administered in both groups in our study.

Keywords: Cardiac surgical procedures; Cardiopulmonary bypass; General anesthesia; Ketamine; Propofol; Neuroprotective Agents

Introduction

Despite remarkable progress in surgical, Cardio Pulmonary Bypass (CPB) and anesthetic techniques, neurocognitive damage still remains an important cause of postoperative morbidity in cardiac surgery [1,2]. The aetiology of neurocognitive damage is likely to be multifocal; including macro and micro emboli, cerebral hypoperfusion, inflammation and nonpulsatile flow [3,4].

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Ketamine reduces postischemic neuronal cell loss in the cortex, directly suppresses proinflammatory cytokine production and improves neurological outcome after cerebral ischemia in rats [5]. Demonstrated that S (+)-ketamine protects neurons after glutamate damage and a small beneficial effect on cognitive performance with ketamine, also a N-methyl-D-aspartic Acid (NMDA)-receptor antagonist, after cardiac surgery [6]. We planned to assessing the neurocognitive function effects of ketamine to 50 patients undergoing coronary artery bypass surgery (CABS), using repeated Mini Mental Test (MMSE) as indicative of cognitive disfunction.

Materials 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 Ethical Review Committee. We considered all patients aged between 58 and 76 years who were referred to a single cardiothoracic surgical team for elective, primary coronary revascularization. Patients were excluded from the study for the following reasons: a history of neurological (including previous transient ischemic attacks, stroke, and seizures), psychiatric, gastrointestinal, hepatic, renal or hematologic and clotting systems disorder; evidence within the previous 2 years of drug abuse (prescribed or non-prescribed) or regular use of anti epileptics, antidepressants and emergency cases and repeat procedures. Patients undergoing Cardio Pulmonary Bypass (CPB) were randomized 2 groups: Group 1 (ketamine) (n=25) or Group 2 (propofol) (n=25) in a double-blind manner at the time of induction of general anesthesia. In the propofol group, anesthesia was induced with 3 mg/kg propofol, 1 µg/kg remifentanyl, 0.1 mg/kg vecuronium. Remifentanyl 0.5 µg/kg/min to 1 µg/kg/min was infused intravenously throughout the whole procedure. In the ketamine group, anesthesia was induced with 1 mg/kg to 2 mg/kg propofol, 1 mg to 2 mg ketamin, 0.1 mg/kg vecuronium. Ketamin 1 mg/kg/hr was infused intravenously. 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 systemic hypoxemia. Standard physiological monitoring Electrocardiogram (ECG), arterial pressure, central venous pressure, nasopharyngeal temperature, Fraction of Inspired Oxygen (FiO₂), End-Tidal Carbon Dioxide Concentration (ETCO₂), airway pressure, Peripheral O₂ Saturation (PerSaO₂), and urine output was used throughout the procedure. CPB was established with a flatbed membrane oxygenator with a cardiomy reservoir/filter and 2 or 3 low-pressure cardiomy suckers. Moderate hypothermia (32°C) was used during CPB. Pump flow was adjusted to achieve 2.4 L • min⁻¹ • m at 37°C and 1.8 L • min⁻¹ • m at 32°C. Mean Arterial Pressure (MAP) was maintained between 50 mmHg and 60 mmHg. In 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.

Cognitive function was measured using Mini-Mental State Examination (MMSE) on day before surgery and three days later. (Scale: A). Statistical evaluations were made using SPSS for Windows (SPSS 11.5 for Windows). The change in scores for MMSE (preoperative and postoperative) was calculated for each patient and for all the group and the results were compared statistically with paired simple t-test.

Results

Seventy consenting patients were randomized from a consecutive

Table 1: Baseline Patient Data.

	Group 1	Group 2	P
Age (year)	63+/-4	68+/-6	0,720
CBP duration (minute)	154+/-25	141+/-33	0,614
Lowest temperature (degrees C)	3+/-3	30+/-4	0,786

Values are means ± SD. P>0.05 indicates no statistically significant difference

Table 2: Baseline Patient Data and Scores for Mini- Mental State Examination.

	1. MMSE (0-30)	2. MMSE (0-30)	P
Group 1	19,2	18,3	0,663
Group 2	17,6	15,3	0,571

P>0.05 indicates no statistically significant difference

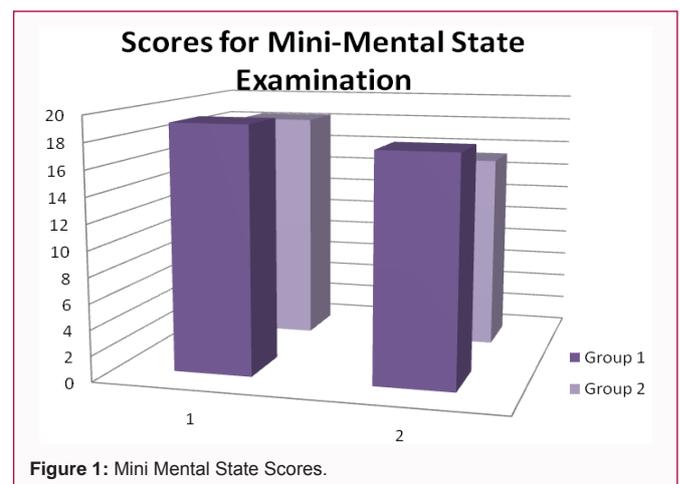


Figure 1: Mini Mental State Scores.

series over a 2-year period before randomization, 20 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. Fifty patients completed both tests. The two groups were comparable with respect to demographics and MMSE Scores.

The mean age, CBP duration, lowest temperature was not statistically significant (Table1). Biochemical, hematologic, and clotting screen data both before and after surgery showed no differences. Peroperative and postoperative blood pressures and pulse rates showed differences between groups. Peroperative nasopharyngeal temperatures and pump flow rates showed no differences between groups. The ECG monitoring revealed that most patients remained in sinus rhythm, again with no difference between groups.

Discussion

Neurologic complications following CPB may be as high as 40% [1,7]. 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 unable to repair from injury once it has occurred [3,4,8]. In the early 1950s experimental models of CPB showed promise, but initial human trials were disappointing. In just 60 years CPB has progressed from a risky laboratory experiment to an event occurring many times

Orientation	
What is the (year) (season) (date) (day) (month)?	5 <input type="checkbox"/>
Where are we: (country) (city) (part of city) (number of flat/house) (name of street)?	5 <input type="checkbox"/>
Registration	
Name three objects: one second to say each. Then ask the patient to name all three after you have said them. Give one point for each correct answer. Then repeat them until he learns all three. Count trials and record.	3 <input type="checkbox"/>
TRIALS	
Attention and calculation	
Serial 7s: one point for each correct. Stop after five answers. Alternatively spell 'world' backwards.	5 <input type="checkbox"/>
Recall	
Ask for the three objects repeated above. Give one point for each correct.	3 <input type="checkbox"/>
Language	
Name a pencil and watch (two points). Repeat the following: 'No ifs, ands or buts' (one point). Follow a three-stage command: 'Take a paper in your right hand, fold it in half and put it on the floor' (three points). Read and obey the following: Close your eyes (one point). Write a sentence (one point). Copy a design (one point).	9 <input type="checkbox"/>
Total score	

Scale A: Mini Mental State Examination.

daily through the world. Unfortunately, in this time, the reported incidence of clinical neuropsychiatric dysfunction after CPB varies considerably. Despite numerous technical advances, neurologic and neuropsychiatric dysfunction continues to be significant and undeniable risks of cardiac surgery [9]. 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 [10]. Although controversial, prophylactic thiopental infusions (completely suppressing electroencephalographic activity) immediately prior to and during intracardiac procedures have been reported to decrease the incidence and severity of neurologic deficits. Propofol may reduce the delivery of micro emboli to the cerebral circulation by decreasing the cerebral blood flow [11]. Propofol has a direct neuroprotective effect *in vitro*, although Roach et al. could not demonstrate a protective effect of propofol during open-heart surgery [12]. Propofol enhances the anti-inflammatory response to surgery by several mechanisms. Studies suggest that magnesium may also be beneficial [13]. The role of calcium channel blockers (nimodipine and nicardipine) and N-methyl-D-aspartate (NMDA) antagonists (ketamine) remains largely investigational [14]. Although controversial, calcium channel blockers and N-methyl-D-Aspartate (NMDA) antagonists have been reported to decrease the incidence and severity of neurologic deficits [15]. It had been found 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 [16,17]. Maximal neuroprotection occurred in the animal studies when the drug was administered before the onset of cerebral ischemia. The effect of glutamate in this context highlights the possibility of further reducing the morbidity of CABS. 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.

The MMSE is a good instrument for assessing cognitive function, but takes up to 10 minutes and cannot fit easily into a standard consultation (Scale: A) [18,19]. Weissrock S, et al. [20] suggested the MMSE could be systematically integrated to the pre and postoperative screening. In this study, cognitive function was measured using Mini-Mental State Examination. We could not demonstrate that intraoperatively administered ketamine resulted in greater neuroprotective effects. This might have masked a neuroprotective effect of ketamine because propofol was administered in both groups in our study. Propofol may reduce the delivery of micro emboli to the cerebral circulation by decreasing the cerebral blood flow. Propofol enhances the anti-inflammatory response to surgery by several mechanisms. Ketamine in combination with propofol during cardiac surgery is associated with a stable hemodynamic profile.

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