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Importance of Erythropoietin in Brain Protection after Cardiac Surgery: A Pilot Study

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ABSTRACT

Background: Neurologic complications after cardiac operations present an important medical problem, as well as a financial burden. They increase the morbidity and hospital stays of patients who have otherwise undergone successful heart operations. The current protocols for perioperative brain protection against ischemic events are not optimal. Because of its different pleiotropic mechanisms of action, recombinant human erythropoietin might provide neuroprotection.

Methods: In this study, we included 20 patients who were older than 18 years and required surgical revascularization of the heart with the use of the heart-lung machine. Ten patients received 3 consecutive intravenous doses (24,000 IU) of recombinant human erythropoietin (rHuEpo). Neurologic and magnetic resonance imaging (MRI) examinations were done before and in the first 5 days after surgery.

Results: The erythropoietin-treated and control groups were comparable with respect to study protocol outcomes: number of coronary artery bypass grafts (3.3 and 3.2 grafts/patient, respectively), operative time (4.12 and 4.6 hours), and transfusion volume per patient (708 and 674 mL). The groups were also comparable with respect to blood pressure values at all stages of the operation. MRI scans revealed that 4 of 10 patients from the control group had fresh ischemic brain lesions after open heart surgery. None of the patients in the erythropoietin-treated group had fresh ischemic brain lesions.

Conclusion: Although the number of patients was small, the results regarding brain protection with rHuEpo are encouraging. rHuEpo is a promising neuroprotective agent.

INTRODUCTION

The heart-lung machine (HLM) has been used in cardiac surgery since H. Gibbon, Jr. introduced it in 1953 [Gibbon 1968]. Despite the enthusiasm that so-called off-pump procedures have brought to cardiac surgery, approximately 80% of such surgeries are still performed with the use of the HLM [Ferguson 2002]. Technological improvements in the HLM have enabled open heart surgery to be safely performed on older patients, who may have concomitant diseases. Other known risk factors are female sex, systolic hypertension, cerebrovascular insult, diabetes, and atherosclerosis of the ascending aorta [Roach 1996; van Diyk 2000; Newman 2001]. Among the most serious and frequent complications of cardiac surgery are neurologic complications that might increase morbidity, mortality, and length of hospital stay. Such complications also have an impact on hospital costs. At the same time, neurologic complications decrease the patient's quality of life, regardless of the success of the heart surgery operation. The incidence of brain stroke is 1% to 5% according to the literature [Jönsson 1999; Herrmann 2000], and delirium occurs in 10% to 30% of cases [Donato 1992]. Cognitive dysfunction is recognized in 33% to 83% of patients after open heart operation [Kilminster 1999].

The current protocols for perioperative brain protection against ischemic events are not optimal. Hypothermia during cardiac surgery protects against brain ischemia; however, some alterations of the coagulation cascade and the inflammatory response occur during hypothermia. A recently proposed protocol combines mild intraoperative hypothermia with peripheral active warming to avoid the need for fast, intense rewarming and thus minimize the potential for brain damage [Campos 2008]. Furthermore, although arterial line filters prevent passage of particles larger than 20 to 40 μm, smaller particles produced by embolization in distal vessels may still cause transient or permanent neurologic disorders.

A steadily growing body of evidence indicates that the therapeutic benefits of recombinant human erythropoietin (rHuEpo) could extend far beyond the treatment of anemia [Rath 2009]. Several recently published reports have described tissue-protective nonhematologic effects of rHuEpo that can prevent ischemia-induced tissue damage in several organs. The protective effects of rHuEpo on central and peripheral neurons, cardiomyocytes, hepatocytes, vascular endothelial cells, the pancreas, and the uterus have been proved [Nagal 2001; Timmer 2009; Xiong 2009]. Several mechanisms of rHuEpo neuroprotection have been recognized, including (1) decreasing glutamate toxicity, (2) inducing the generation of neuronal antiapoptotic factors, (3) reducing inflammation,

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Table 1. Baseline Characteristics of the Study Participants by Study Group

Characteristic	Erythropoietin-Treated Group	Control Group
Median age (range), y	75.5 (71-86)	73.6 (64-82)
Female sex, n	3	5
Blood pressure, mm Hg		
Systolic	130-185	140-190
Diastolic	70-95	60-95
Diabetes, n	4	4
Carotid disease (<70% stenosis), n	3	2
Carotid disease (>70% stenosis), n	1	0
Hyperlipidemia, n	4	4
Body mass index, kg/m^2	29.4	30.3
Peripheral arterial disease, n	1	0
Chronic atrial fibrillation, n	0	2
Current smoker, n	2	0

(4) decreasing nitric oxide–mediated injury, and (5) direct antioxidant effects [Juul 2002; Sasaki 2003; Noguchi 2007].

In a multicenter double-blinded placebo-controlled study of patients with ischemic stroke, Ehrenreich et al [2002] found a reduction in infarct size and a better clinical outcome in patients treated with rHuEpo. According to the evidence, erythropoietin functions as a multipotent tissue protector in the heart [Parsa 2003, van der Meer 2005] and in the central nervous system [Sakanaka 1998; Wang 2004; Noguchi 2007].

The purpose of the present study was to find out whether pre-, peri-, and postoperative intravenous administration of rHuEpo has any influence on the development of transient or permanent neurologic dysfunction in patients undergoing open heart surgery.

We have hypothesized that the administration of rHuEpo to patients who will undergo open heart surgery reduces the risk for transient or permanent neurologic dysfunction.

PATIENTS AND METHODS

In this study, we included 20 patients who were older than 18 years and required surgical revascularization of the heart with the use of the HLM. Table 1 summarizes the characteristics of the study group. All of the patients signed a written consent form approved by the State Ethical Committee. Patients with known malignant hypertension, cancer, hematologic disorders, or chronic renal insufficiency, who were already receiving rHuEpo therapy, or who had a known allergy to the medications were excluded from the study. A neurologist performed a thorough neurologic examination before the operation. A confusion assessment was performed 24 and 48 hours after surgery [Inouye 1990]. The patient rHuEpo protocol consisted of 3 consecutive doses (24,000 IU) of epoetinum alfa (Eprex; Janssen-Cilag, Turnhout, Belgium) administered intravenously. The first dose was given 1 day before the procedure, the second dose was administered on the day of operation, and the third dose was given 1 day after completion of the surgery. After induction of anesthesia with fentanyl, Norcuron (vecuronium bromide), and etomidate, inhalation anesthesia with isoflurane followed until extracorporeal circulation began, after which propofol was administered intravenously. Cannulas for antegrade and retrograde cardioplegia were used, the depth of the latter being controlled with transesophageal echocardiography. All patients were cooled to an esophageal temperature of 35°C. The arterial pressure, the duration of cardiac arrest, and the duration of extracorporeal circulation were recorded along with other data. After the operation, patients were transferred to the intensive care unit ward, where the anesthesiologist on duty closely monitored the patient's neurologic status. All deviations were recorded. A clinical neurologist performed another neurologic examination on the first and second postoperative days.

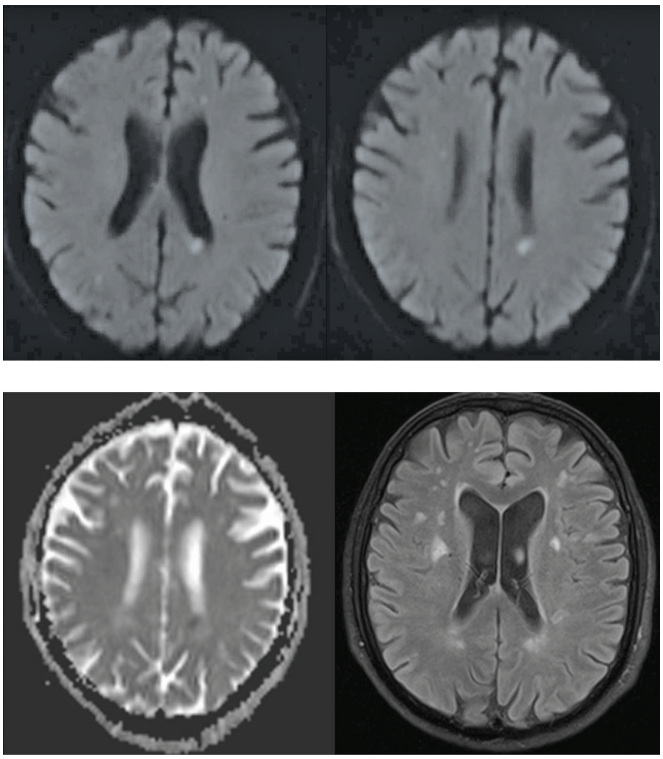

Figure 1. Diffusion-weighted and fluid-attenuated inversion recovery magnetic resonance imaging of a 72-year-old man. A postoperative scan performed 3 days after surgery revealed 5 new diffusion-weighted lesions. One lesion was located in the white matter of the left occipital lobe (5 mm), 3 lesions (2 mm) were located in the left frontal lobe, and 1 lesion (2 mm) was located in the gray matter of the right occipital-parietal region. These lesions were consistent with small embolic infarctions.

Magnetic Resonance Imaging

A magnetic resonance imaging (MRI) examination was performed in all patients of the study group 24 hours before

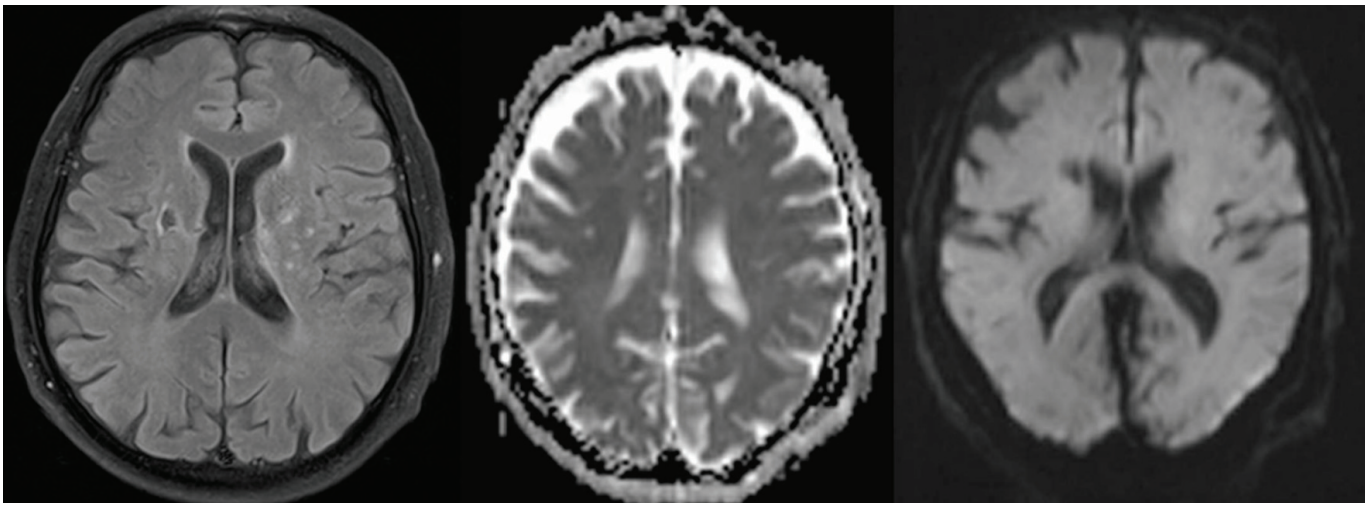

Figure 2. Diffusion-weighted and fluid-attenuated inversion recovery magnetic resonance imaging of a 75-year-old man. Preoperative scans depicted old ischemic lesions bilaterally in white matter. No diffusion abnormalities were seen on the postoperative scan.

surgery and a median of 4 days (range, 2-5 days) after surgery. MRI studies were obtained on a 3T instrument (Magnetom Trio TIM; Siemens, Erlangen, Germany) with standardized protocols [Knipp 2004; Stolz 2004; Barber 2008]. Scans were always performed in the same order with a T1-weighted 3-plane localizer, a diffusion-weighted imaging (DWI) sequence, and a fluid-attenuated inversion recovery (FLAIR) sequence. DW images were obtained with a multislice, single-shot spin-echo echo planar image sequence. Slice thickness was 5 mm with a 0.5-mm gap, with the number of slices set to include the entire brain. The matrix size was 128 × 128, the field of view was 230 mm, and the repetition/echo time (TR/TE) was 4000/83 milliseconds. The diffusion gradient strength was varied between 0 and 45 mT/m, resulting in 2b values of increasing magnitude from 0 to 1000 seconds/mm. FLAIR images were obtained with a slice thickness of 5 mm with a 0.5-mm gap, with the number of slices set to include the entire brain. The matrix size was 204 × 256, the field of view was 220 mm, the TR/TE was 9000/94 milliseconds, and the inversion time, TI, was 2500 milliseconds. The images were presented to one of the investigators blinded to the results of the clinical assessments, and the postoperative MRI scans were analyzed for the presence and number of ischemic lesions. These results were compared with those for preoperative MRI scans.

RESULTS

Twelve male and 8 female patients were included in the study. None of them had significant carotid lesions. All patients underwent complete coronary artery revascularization. The baseline characteristics of the rHuEpo-treated and nontreated groups were comparable (Table 1). The outcomes of the 2 groups were comparable for all observed parameters: the number of coronary artery bypass grafts, anesthesia duration, blood pressure, and transfusion volume (Table 2). All of the patients survived open heart surgery. No patient showed neurologic dysfunction before the operation, and only 2 of the patients in the untreated group experienced delirium. Both patients had MRI-detectable brain changes. MRI evaluations performed 24 hours before surgery revealed multiple ischemic lesions in all of the patients. The lesions were all small, 2 to 5 mm in diameter. Some of the lesions in the border zone between the middle cerebral artery and the anterior cerebral artery were confluent. Only 1 patient had a large ischemic region in the left middle artery circulation. Four (40%) of the 10 participants without rHuEpo therapy showed new cerebral infarction in the postoperative DWI sequence (Figure 1). Two of 4 patients with postoperative ischemia had small lesions (approximately 2 mm in diameter); the other 2 patients had ischemic lesions larger than 5 mm (Figure 1). The distribution of the DWI lesions was as follows: the middle cerebral artery (61%), the border zone between the middle cerebral artery and the anterior cerebral artery (31%), and the posterior circulation (8%); 76% of the ischemic lesions were on the left. DWI lesions occurred in more than 1 vascular territory in all patients with multiple lesions. We observed no fresh ischemic lesions on DWI images in the 10 patients treated with rHuEpo prior to surgery (Figure 2).

DISCUSSION

Among the most serious and frequent complications of cardiac surgery are neurologic complications. Current protocols for perioperatve brain protection against ischemic events are not optimal. rHuEpo has been used successfully and safely in renal anemia patients, cancer patients with anemia, and as a part of optimized blood-management protocols for reducing homologous blood transfusions [Noguchi 2007; Rath 2009; Terrovitis 2009]. An important discovery that has led us toward new treatment modalities is that erythropoietin is a pleiotropic tissue-protective cytokine [Parsa 2003; van der Meer 2005]. Erythropoietin production has been found in the peripheral and central nervous system,

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Table 2. Outcome according to Study Protocol*

End Point	Erythropoietin-Treated Group	Control Group	P†
Operative death	0	0	
Cerebrovascular insult, n	0	2	.0001
No. of CAB grafts	3.3	3.2	.81
Operative time, n	4.12	4.6	.53
ECC, min	95.8	86.1	.47
Cardiac arrest, min	67.9	63.4	.68
Mean blood pressure, mm Hg			
Preoperative	145/71	147/66	.64
During operation (systolic)	>60	>60	
Postoperative	135/66	142/68	.47
Lactate after ECC, mmol/L	1.53	1.71	.42
Troponin I (preoperative), ng/mL	0.301	0.256	.56
Troponin I (postoperative), ng/mL	0.988	0.75	.43
Transfusion, mL/patient	708	674	.54

*CAB indicates coronary artery bypass; ECC, extracorporeal circulation.
†Two-tailed test.

where it exhibits a neuroprotective and anti-inflammatory action [Sakanaka 1998; Kidd 2009]. In a multicenter double-blinded placebo-controlled study of patients with ischemic stroke, 3 sequential intravenous doses of 33,000 IU reduced the size of the infarct compared with the placebo group [Ehrenreich 2002]. In addition, numerous research groups have reported an antiapoptotic effect on cardiomyocytes and confirmed a positive influence of systemic rHuEpo administration in cardiac and neural protection against ischemia/reperfusion injury [Moon 2003; Fletcher 2009]. We therefore decided to test the effects of intravenous rHuEpo in protecting the brain after cardiac surgery. We administered 3 consecutive doses (24,000 IU) of Eprex intravenously. The first 2 doses were given before surgery, and the third was administered on the day after completion of surgery. The manner in which rHuEpo was administered in our study might produce an rHuEpo level in blood and tissue that could potentially provide tissue protection. In the presented study, we examined rather crude clinical parameters of brain injury: neurologic examination and MRI results. According to the MRI images, however, we clearly found that the patients treated with rHuEpo had no fresh ischemic lesions, in contrast to the nontreated group. We stress that the 2 patient groups were comparable not only with respect to their basic characteristics but also with regard to procedural ones (Tables 1 and 2). Erythropoietin treatment restores brain mitochondrial function after traumatic brain injury [Junk 2002; Parsa 2003; Xiong 2009]. It enhances cellular energy generation and reduces oxidative stress. The effects of erythropoietin might also be important for protecting the brain after open heart surgery.

CONCLUSION

In this pilot study, our study group was small. We conclude that the results regarding brain protection with rHuEpo are encouraging and promising. rHuEpo is recognized as a promising neuroprotective agent. The effects on long-term clinical outcome are to be followed up. The correlations between MRI results, neurologic outcome, and brain and heart injury biomarkers should also be tested.

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