The Erythropoietin NeuroProtective Effect: Assessment in CABG Surgery (TENPEAKS)

A Randomized, Double-Blind, Placebo Controlled, Proof-of-Concept Clinical Trial

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Background and Purpose—Neurocognitive dysfunction complicates coronary artery bypass surgery. Erythropoietin may be neuroprotective. We sought to determine whether human recombinant erythropoietin would reduce the incidence of neurocognitive dysfunction after surgery.

Methods—We randomly assigned 32 elective first-time coronary artery bypass graft patients to receive placebo or 375 U/kg, 750 U/kg, or 1500 U/kg of recombinant human erythropoietin divided in 3 daily doses, starting the day before surgery. Primary outcomes were feasibility and safety, and secondary outcomes were neurocognitive dysfunction at discharge and 2 months.

Results—All subjects were male, mean age 60 years (range 46 to 73). No significant differences were found in pump time, cross-clamp time, or hospital length of stay. Mortality and pure red cell aplasia were not observed. One patient in the 375 U/kg group had ST changes compatible with myocardial injury immediately postoperative, but no other thrombotic complications were observed. Neurocognitive dysfunction occurred in 21/32 (66%) of patients at discharge and 5/32 (16%) at 2 months. Neurocognitive dysfunction at discharge by group was: placebo 6/8 (75%), 375 U/kg 4/8 (50%), 750 U/kg 6/8 (75%), and 1500 U/kg 5/8 (63%). Neurocognitive dysfunction at 2 months by group was: placebo 3/8 (38%), 375 U/kg 1/8 (13%), 750 U/kg 1/8 (13%), and 1500 U/kg 0/8 (0%). Neurocognitive dysfunction at 2 months for erythropoietin at any dose was 2/24 (8.3%) versus 3/8 (38%) for placebo ($P=0.085$).

Conclusions—This study demonstrates feasibility and safety for the use of human recombinant erythropoietin as a neuroprotectant in coronary artery bypass graft surgery. A trend in the reduction of neurocognitive dysfunction at 2 months was associated with erythropoietin use. A multicenter randomized controlled trial is warranted. (Stroke. 2009; 40:2769-2775.)

Key Words: neuroprotective agents ▪ coronary artery bypass ▪ recombinant erythropoietin
Moreover, rHuEpo crosses the blood brain barrier to mitigate the clinical effects of cerebral damage in animal models of stroke, inflammation, trauma, and seizures. Two human pilot studies suggest the antiapoptotic effects of rHuEpo may improve clinical outcomes in stroke and in neurocognitive dysfunction associated with chemotherapy. Indeed, rHuEpo therapy reduces the neurocognitive dysfunction associated with dialysis, although this effect has historically been attributed to increasing the hematocrit. We hypothesized that rHuEpo would reduce the incidence of NCD after CABG surgery. We conducted a double-blind, randomized, placebo-controlled, pilot study in 32 first-time CABG patients to investigate the feasibility, safety, and treatment effect of 3 doses of rHuEpo given the day before, the time of, and the day after surgery. The randomization key was prepared by a physician independent from the study enrollment. Consecutive patients were recruited between September 2004 and March 2005 at the Foothills Medical Centre, a tertiary academic hospital. Two-month follow-up of the last patient occurred in May 2005. Inclusion and exclusion criteria are listed in Table 1. Patients were randomized by random number generator to receive placebo or a total of 375 U/kg, 750 U/kg, or 1500 U/kg of rHuEpo (Eprex, Ortho Biotech) intravenously divided in 3 divided doses: the day before, at the time of, and the day after surgery. The randomization was prepared by a physician independent from the study and held by an independent study pharmacist who prepared the study drug. Investigators, patients, and the medical team were blinded to treatment allocation using a triple dummy design. The information was available for unblinding if the medical team deemed it necessary for patient care. Hemoglobin levels were not expected to lead to unblinding, because a clinically significant erythropoietic effect of rHuEpo requires longer than the standard 5- to 7-day admission after CABG surgery. Blinding was maintained until after the last neurocognitive test was scored.

The morning of surgery, patients received their usual antianginal medication. Lorazepam, 1 mg sublingual, was given for anxiolysis, and ACE inhibitors and angiotensin receptor blockers were held. The study drug was given intravenously 16 to 24 hours before the operation, repeated in the operating room before the initiation of bypass, and then again the day after surgery. Sedation, intubation, use of pulmonary artery catheters, addition of a spinal anesthetic, antifibrinolytics, and neuromuscular blockade were at the discretion of the anesthetist and surgeon. Transesophageal echocardiography was performed on all patients, as per standard operative room practice at our institution, to assess cardiac function, visualize and grade aortic atheroma, and to ensure adequacy of deair maneuvers before weaning from cardio-pulmonary bypass (CPB). Mild hypothermic CPB (32 to 34°C) was used in all patients, PaCO2 maintained at 35 to 40 mm Hg (o-stat management), and mean arterial pressure (MAP) maintained between 50 and 90 mm Hg. Temperature was allowed to drift downwards without active cooling, and rewarthing did not exceed 37°C. Isoflurane was maintained at <0.5%, and MAP controlled with isoflurane, propofol, and vasoactive agents at the discretion of the anesthetist. Blood cardioplegia was administered at the discretion of the cardiac surgeon. For all patients receiving proximal grafts, a single cross clamp was used. Patients consenting to transfusion received packed red blood cells if the hematocrit was less than 20%, if the mixed venous saturation was less than 70%, and the surgeon and anesthetist agreed transfusion was indicated. Postoperatively, patients were transferred to the Cardiovascular Intensive Care Unit on a propofol infusion, and managed with the goals of hemodynamic stability, analgesia, and early extubation by means of a weaning pathway. All patients receive ASA 325 mg 6 hours postoperatively if there was no contraindication.

Patients underwent 10 neurocognitive tests (Table 2), the Folstein Mini-Mental test, the Beck Anxiety and Depression scales, and a full neurological examination preoperatively (no more than 1 month before surgery), on the day of discharge, and during the 2-month follow-up with the cardiac surgery clinic. Patients who did not attend the follow-up clinic were tested at home. The tests conform to the 1995 Statement of Consensus on Assessment of Neurobehavioural Outcomes After Cardiac Surgery, and were performed by a blinded, trained neuropsychometrist.

**Statistical Analysis**

The primary outcomes were feasibility and safety, including recruitment rates, 28-day all-cause mortality, ICU and hospital length of stay (LOS), incidence of pure red cell aplasia (PRCA), and incidence of thrombotic complications (stroke, myocardial infarction [MI], deep vein thrombosis, and pulmonary embolism). The secondary outcomes for this trial were incidence of NCD at discharge and at 2-month follow-up post-CABG, among study arms and between placebo and rHuEpo at any dose. We prospectively assigned unfinished or missing test values postoperatively to be substituted by the score from the other postoperative time point, or the preoperative value if no other value was available. All patients were included in the final analysis in the groups in which they were randomized according to the intention-to-treat principle. The postoperative neurocognitive tests were compared to preoperative baseline tests to determine decline, using patients as their own controls. A priori, we defined NCD as a 20% reduction in 20% of the neurocognitive tests.

Analysis of continuously normally distributed variables within and between groups were undertaken using the appropriate Student t test. Nonnormally distributed continuous variables were analyzed using the Mann–Whitney U test. Categorical variables were analyzed using Fisher exact test. A probability value of less than 0.05 was considered significant. All statistical tests were 2-sided. Given the exploratory nature of this analysis, no correction was made for multiple comparisons.
Table 2. Neurocognitive Assessments

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>a. Vocabulary subtest (WAIS III)*</td>
</tr>
<tr>
<td>Assessment of verbal and general mental ability, testing both recall and speaking vocabulary. A list of 35 words in increasing difficulty is read to the patient as “what does ___ mean,” and the test is continued until the patient fails 5 words consecutively or the list is exhausted. The subject receives 1 or 2 points per acceptable definition depending on accuracy, precision, and aptness.</td>
</tr>
<tr>
<td>b. Hopkins verbal learning test* (HVLT-R)</td>
</tr>
<tr>
<td>Six different forms are available to minimize practice effects. The test is administered by reading 12 words aloud and asking the subject to reproduce them, immediately and after a delay. The test has 3 learning trials, a delayed recall trial, and a yes/no recognition trial, where the words are identified from a list including distracters.</td>
</tr>
<tr>
<td>c. Brief visual retention test (BVMT-R)</td>
</tr>
<tr>
<td>Six different forms are available to minimize practice effects. The “stimulus” forms have 6 geometric figures in a 2×3 array. The subject is asked to reproduce the figures in their correct position after 10 seconds exposure. The test has 3 learning trials and, after 25 minutes, a delayed recall trial and a yes/no recognition trial.</td>
</tr>
<tr>
<td>d. Digit symbol substitution test (WAIS III)</td>
</tr>
<tr>
<td>Four rows contain 100 blank squares above which are numbers in random order. The subject is given a key associating numbers with symbols. The score is the No. of correct symbols printed for each No. in 90 seconds.</td>
</tr>
<tr>
<td>e. Trail Making A*</td>
</tr>
<tr>
<td>Simple assessment of coordination, attention, and concentration. Patients connect a series of numbers in order in as short a period of time as possible.</td>
</tr>
<tr>
<td>f. Trail making B*</td>
</tr>
<tr>
<td>More sensitive assessment of visuomotor coordination, attention, and concentration. Like Trail Making A, but alternating numbers and letters in order.</td>
</tr>
<tr>
<td>g. Digit span forwards and backwards (WAIS III)*</td>
</tr>
<tr>
<td>A subject is read sequences of digits and repeats them, with the sequences increasing in length. The process is then repeated, with the patient repeating sequences of numbers in reverse order.</td>
</tr>
<tr>
<td>h. Spatial span forwards and backwards (WAIS III)</td>
</tr>
<tr>
<td>A subject repeats a series of actions forwards and backwards using 10 blocks in 2 dimensions, first beginning with a sequence of 2 actions. The process is then repeated, with the patient reproducing sequences in reverse order.</td>
</tr>
<tr>
<td>i. Grooved pegboard</td>
</tr>
<tr>
<td>Test of complex manipulative dexterity and visuomotor coordination. Pegs with a key along 1 side must be rotated into 25 holes with randomly positioned slots.</td>
</tr>
<tr>
<td>j. FAS oral verbal fluency test</td>
</tr>
<tr>
<td>The subject is asked to produce as many words beginning with a specific letter of the alphabet as possible within 1 minute in 3 separate trials.</td>
</tr>
</tbody>
</table>

Memory

b. Hopkins verbal learning test* (HVLT-R)

Six different forms are available to minimize practice effects. The test is administered by reading 12 words aloud and asking the subject to reproduce them, immediately and after a delay. The test has 3 learning trials, a delayed recall trial, and a yes/no recognition trial, where the words are identified from a list including distracters.

c. Brief visual retention test (BVMT-R)

Six different forms are available to minimize practice effects. The “stimulus” forms have 6 geometric figures in a 2×3 array. The subject is asked to reproduce the figures in their correct position after 10 seconds exposure. The test has 3 learning trials and, after 25 minutes, a delayed recall trial and a yes/no recognition trial.

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Four rows contain 100 blank squares above which are numbers in random order. The subject is given a key associating numbers with symbols. The score is the No. of correct symbols printed for each No. in 90 seconds.

e. Trail Making A*

Simple assessment of coordination, attention, and concentration. Patients connect a series of numbers in order in as short a period of time as possible.

f. Trail making B*

More sensitive assessment of visuomotor coordination, attention, and concentration. Like Trail Making A, but alternating numbers and letters in order.

g. Digit span forwards and backwards (WAIS III)*

A subject is read sequences of digits and repeats them, with the sequences increasing in length. The process is then repeated, with the patient repeating sequences of numbers in reverse order.

h. Spatial span forwards and backwards (WAIS III)

A subject repeats a series of actions forwards and backwards using 10 blocks in 2 dimensions, first beginning with a sequence of 2 actions. The process is then repeated, with the patient reproducing sequences in reverse order.

Concentration and attention

g. Digit span forwards and backwards (WAIS III)*

A subject is read sequences of digits and repeats them, with the sequences increasing in length. The process is then repeated, with the patient repeating sequences of numbers in reverse order.

h. Spatial span forwards and backwards (WAIS III)

A subject repeats a series of actions forwards and backwards using 10 blocks in 2 dimensions, first beginning with a sequence of 2 actions. The process is then repeated, with the patient reproducing sequences in reverse order.

Manual motor performance

i. Grooved pegboard

Test of complex manipulative dexterity and visuomotor coordination. Pegs with a key along 1 side must be rotated into 25 holes with randomly positioned slots.

Frontal lobe function

j. FAS oral verbal fluency test

The subject is asked to produce as many words beginning with a specific letter of the alphabet as possible within 1 minute in 3 separate trials.

Results

Recruitment and allocation are described in Figure 1. The characteristics of the 32 patients studied are listed in Table 3. All subjects were male with a mean age of 60 (range 46 to 73). Mean(±SD) educational background was 11.2 years (±2.4). Hypertension was present in 21/32, diabetes mellitus in 7/32, dyslipidemia in 24/32, CHF in 2/32, and COPD in 2/32. Mean(±SD) pump time was 76 minutes (±23), and cross-clamp time was 56 minutes (±22). The median (inter-quartile range, IQR) number of bypass grafts was 2 (1–3) and the median number of aortic anastomoses 2 (1–3). Median ICU length of stay (LOS) was 1 (1–2) day. Median hospital LOS (IQR) was 6 days (5 to 6.5). Mortality and pure red blood cell aplasia (PRCA) were not observed in any group. One patient in the 375 U/kg group had ST changes compatible with myocardial injury immediately postoperative, but no other thrombotic complications were observed. In discussion with the cardiac surgeon, this was felt secondary to cholesterol emboli because of manipulation of severely diseased arteries at the time of the surgery. NCD was present in 21/32 (66%) of patients at discharge and 5/32 (16%) at 2 months. One patient declined 2-month follow-up, and his best post-operative scores were used for the missing data. That patient did not suffer NCD at discharge. All other patients completed the test batteries, which were well tolerated and completed in a median (IQR) time of 60 minutes (50–65).

Patient and surgical variables are presented in Table 3. Age, diabetes, dyslipidemia, CHF, COPD, and preoperative Beck Depression and Anxiety Scales were not significantly different between those 2 groups, nor were ICU and hospital LOS. The mean (±SD) pump time for patients receiving rHuEpo at any dose was 72 minutes (±22) and for placebo 84 minutes (±27) (P=0.2, mean difference = −12, 95% CI=[−7.5, 30.8]). The mean (±SD) cross-clamp time for patients receiving rHuEpo was 53 minutes (±21) and for placebo 62 minutes (±27; P=0.3). The number of grafts may indicate more aortic manipulation. The median (IQR) number of bypass grafts for rHuEpo versus placebo treated patients were 3 (2.5 to 4) versus 3.5 (2.5 to 4.5), and the median (IQR) number of venous or radial grafts with aortic anastomoses were 2 (1–3) versus 2 (1.5 to 3). They were not significantly different between the groups. Preoperative hemoglobin concentration was not different between those receiving erythropoietin compared to those in the placebo group (P=0.9). However, mean postoperative hemoglobin concentration was significantly higher in patients receiving erythropoietin compared to those receiving placebo (mean [SD] 110 [10] versus 97 [11.4], P=0.005). Transfusion during the hospital stay occurred in 2/8 (25%) of patients receiving placebo compared to 1/24 (4.1%) of patients receiving erythropoietin (P=0.15; relative risk (RR)=0.167; 95% CI=[0.017 to 1.602]). The patient in the 1500 U/kg group required 4 U of packed red blood cells (pRBCs) for mediastinal bleeding but did not require reoperation. One patient in the placebo group required 2 U of pRBCs for a postoperative hemoglobin concentration of 72 g/L and ST changes on ECG (Preoperative hemoglobin 139 g/L). Another patient in the placebo group required 5 U of pRBCs for mediastinal bleeding and was the only patient in the study to undergo reoperation.
The incidence by group of neurocognitive dysfunction is presented in Figures 2 and 3. Neurocognitive dysfunction at discharge by group was: placebo 6/8 (75%), 375 U/kg 4/8 (50%), 750 U/kg 6/8 (75%), and 1500 U/kg 5/8 (63%). The incidence of NCD at discharge for patients receiving rHuEpo at any dose was 15/24 (63%) compared with 6/8 (75%) for placebo (P=0.681; RR=0.833, 95% CI=[0.502 to 1.382]).

Neurocognitive dysfunction at 2 months by group was: placebo 3/8 (38%), 375 U/kg 1/8 (13%), 750 U/kg 1/8 (13%), and 1500 U/kg 0/8 (0%). The incidence of NCD at follow-up for patients receiving rHuEpo at any dose was 2/24 (8.3%) compared to 3/8 (38%) for placebo (P=0.085, RR=0.222, 95% CI=[0.045 to 1.101]).

Discussion

The neurological complications of cardiac surgery can range from acute stroke and frank coma (“type I complications”), to encephalopathy, delerium, and the subtle yet potentially debilitating loss of neurocognitive function (“type II complications”). Little progress has been made to reduce NCD, compromising patients’ productivity, quality of life, and cost of care. In a cohort of 261 CABG patients published in 2001, Newman et al reported incidences of NCD at discharge of 53%, at 6 weeks, 36%, and at 6 months, 24%. Despite this improvement, at 5 years, 42% of patients had a significant long-term loss of neurocognitive function, and the patients at

Table 3. Patient Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Placebo</th>
<th>rHuEpo 375 U/kg</th>
<th>rHuEpo 750 U/kg</th>
<th>rHuEpo 1500 U/kg</th>
<th>rHuEpo Any Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ± SD</td>
<td>60 ± 7.2</td>
<td>62 ± 7.1</td>
<td>61 ± 7.0</td>
<td>57 ± 7.0</td>
<td>60 ± 7.7</td>
<td>59 ± 7.2</td>
</tr>
<tr>
<td>HTN 21/32 (66%)</td>
<td>6/8 (75%)</td>
<td>5/8 (63%)</td>
<td>6/8 (75%)</td>
<td>5/8 (63%)</td>
<td>15/24 (63%)</td>
<td></td>
</tr>
<tr>
<td>DM 7/32 (22%)</td>
<td>1/8 (12.5)</td>
<td>5/8 (63%)</td>
<td>0/8 (0%)</td>
<td>1/8 (13%)</td>
<td>3/24 (13%)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidaemia 26/32 (81%)</td>
<td>7/8 (88%)</td>
<td>7/8 (88%)</td>
<td>6/8 (75%)</td>
<td>7/8 (88%)</td>
<td>20/24 (83%)</td>
<td></td>
</tr>
<tr>
<td>CHF 2/32 (6.4%)</td>
<td>1/8 (13%)</td>
<td>0/8 (0%)</td>
<td>1/8 (13%)</td>
<td>0/8 (0%)</td>
<td>1/24 (4.2%)</td>
<td></td>
</tr>
<tr>
<td>Smoking 16/32 (50%)</td>
<td>4/8 (50)</td>
<td>5/8 (63%)</td>
<td>5/8 (63%)</td>
<td>2/8 (25%)</td>
<td>12/24 (50%)</td>
<td></td>
</tr>
<tr>
<td>COPD 2/32 (6.4%)</td>
<td>0/8 (0%)</td>
<td>2/8 (25%)</td>
<td>0/8 (0%)</td>
<td>0/8 (0%)</td>
<td>2/24 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Pump time ± SD</td>
<td>76 ± 23</td>
<td>84 ± 27</td>
<td>73 ± 27</td>
<td>80 ± 26</td>
<td>65 ± 6</td>
<td>72 ± 22</td>
</tr>
<tr>
<td>Xc time ± SD</td>
<td>56 ± 22</td>
<td>63 ± 27</td>
<td>57 ± 26</td>
<td>58 ± 23</td>
<td>46 ± 9</td>
<td>53 ± 21</td>
</tr>
<tr>
<td>ICU LOS (IQR)</td>
<td>1 (1–2)</td>
<td>2 (1–2)</td>
<td>1.5 (1–2)</td>
<td>1 (1–1)</td>
<td>1 (1–1.5)</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td>Hospital LOS (IQR)</td>
<td>6 (5–6.5)</td>
<td>6 (5–6.5)</td>
<td>6 (5–6)</td>
<td>6 (5.5–7.5)</td>
<td>5.5 (4.5–6.5)</td>
<td>6 (5–6)</td>
</tr>
<tr>
<td>Hgb pre-op ± SD</td>
<td>149 ± 8</td>
<td>149 ± 11</td>
<td>150 ± 9</td>
<td>151 ± 8</td>
<td>147 ± 7</td>
<td>149 ± 8</td>
</tr>
<tr>
<td>Hgb discharge ± SD</td>
<td>107 ± 12</td>
<td>97 ± 11</td>
<td>107 ± 10</td>
<td>110 ± 11</td>
<td>114 ± 11</td>
<td>110 ± 10</td>
</tr>
<tr>
<td>Crt pre-op ± SD</td>
<td>85 ± 12</td>
<td>83 ± 7</td>
<td>84 ± 14</td>
<td>79 ± 9</td>
<td>94 ± 13</td>
<td>86 ± 13</td>
</tr>
<tr>
<td>Crt discharge ± SD</td>
<td>83 ± 12</td>
<td>79 ± 11</td>
<td>86 ± 17</td>
<td>85 ± 9</td>
<td>82 ± 12</td>
<td>84 ± 13</td>
</tr>
<tr>
<td>Post-op Afib 4/32 (13%)</td>
<td>2/8 (25%)</td>
<td>1/8 (13%)</td>
<td>1/8 (13%)</td>
<td>0/8 (0%)</td>
<td>2/24 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Transfusion 3/32 (9.3%)</td>
<td>2/8 (25%)</td>
<td>0/8 (0%)</td>
<td>0/8 (0%)</td>
<td>1/8 (13%)</td>
<td>1/24 (4.2%)</td>
<td></td>
</tr>
</tbody>
</table>

HTN indicates hypertension; DM, diabetes mellitus; Xc, cross clamp time (min); LOS, length of stay (median [IQR] days); Hgb, haemoglobin (g/L); Crt, creatinine (μmol/L).
highest risk were those who suffered NCD at discharge. These patients also reported a poorer quality of life, and fewer returned to full-time work.4

Although the pathogenesis of NCD remains unclear, several factors have been implicated. Manipulation of the aorta releases cholesterol emboli. Air emboli may also complicate placement of proximal grafts as well. Indeed, the number of particles has been associated with the frequency of NCD, and using ultrasound guidance in the placement of surgical catheters to avoid cholesterol accumulations can reduce neurological complications.23–25 The bypass pump also results in emboli, both air bubbles and small clots from activation of platelets and coagulation.26,27 On-pump cardiac surgery causes inflammation and may confound hypoxic injury itself. Indeed, not only does the cardiopulmonary bypass pump cause complement activation and elevations in proinflammatory cytokines,2 but plasma from on-pump CABG patients induces apoptosis of cultured endothelial cells.28 Much like in many models of cerebral injury, impaired blood flow, inflammation, and ultimately tissue hypoxia seem to be linked to NCD.

Erythropoietin (Epo), a 35,000-Dalton glycoprotein, was originally discovered as the primary factor stimulating red blood cell production by the bone marrow. However, the first surprising observation in 1994 that both the cytokine and its receptor are expressed in human cultured neurons9 has led to the discoveries that Epo is an antiapoptotic neuron growth factor and that Epo and EpoR are upregulated by Hypoxia Inducing Factor 1 (HIF-1) during oxidative stress, hypoxia, hypoglycemia, and glutamate toxicity.10,13,29 In rodent models of ischemic stroke, brain trauma, inflammatory encephalitis, and chemically induced seizures, rHuEpo crosses the blood brain barrier, reduces neuron cell death, and dramatically attenuates clinically relevant injury.11,14 The protective effect is greatest when the drug is given before or at the time of the injury, but the window of benefit extends for up to 6 hours thereafter. In human patients, rHuEpo treatment is associated with a significant dose-related improvement in cognitive testing in dialysis patients, historically attributed to normalizing the hematocrit.17–19 The Goettingen Epo-Stroke Trial, a randomized, double-blind, proof-of-concept study in 40 patients presenting within 8 hours of a stroke, found rHuEpo significantly reduced serum levels of S-100 Beta, a prognostic marker of neurological injury, and showed a trend to improved stroke scale scores and reduced infarct size.8 In another pilot study in breast cancer patients, rHuEpo therapy was associated with a trend to improvement in cognition, mood, and quality of life.16

Concern remains regarding rHuEpo side effects. Complications include hypertension, seizures, thrombotic vascular events, and pure-red-cell aplasia (PRCA). Prothrombotic effects of Epo, possibly by increasing blood viscosity, increasing platelet production, and inducing the endothelium to increase platelet aggregation, were first raised because of an increase in arteriovenous shunt thrombosis in dialysis patients. Investigations of rheology, hemostasis, and fibrinolysis,29,30 2 meta-analyses of rHuEpo for perioperative reduction of allogenic blood exposure,32,33 and a randomized controlled trial of 1302 critically ill patients34 have not found clear evidence of increased thrombotic risk. However, although short-term use in acute indications may appear safe at present, chronic use in cancer patients may lead to intravascular thrombosis and fatalities.35,36 Lastly, although developing antibodies against endogenous Epo has always been a remote risk in chronic use, a recent surge of cases of PRCA has been associated with subcutaneous use in dialysis patients.37 It appears inadequate storage of preloaded syringes lacking Teflon coating can allow plastic byproducts to leach into the drug to act as an adjuvant, although some discord regarding that mechanism exists in the literature.38–40

**Figure 2.** Incidence of NCD at discharge and 2-month follow-up by group.

**Figure 3.** Incidence of NCD at discharge and 2-month follow-up: placebo vs rHuEpo at any dose.
Our data of short-term rHuEpo therapy to reduce NCD in CABG patients demonstrate that our study protocol is feasible and safe. We completed recruitment of 32 patients at 1 center in the predicted 6 months, and all patients tolerated our test battery well. One patient (1/32, 3.1%) was lost to 8-week follow-up. No complications attributable to rHuEpo were found. Although we had a small sample size, rHuEpo at any dose was associated with a trend to benefit in NCD at 2 months. No effect was seen at discharge, suggesting that if there are indeed benefits from rHuEpo therapy, they take more than 5 days to appear, or that other issues dominate the discharge test performance, like fatigue, pain, opiates, and benzodiazepines.

There are several limitations to our study. First, like all pilot trials the sample size is small. Second, although we prospectively defined NCD as a 20% drop in 20% of neurocognitive tests because of our sample size and used multiple forms for 3 of the tests, practice effects can reduce the sensitivity of this measure. Nevertheless, in at least 1 comparative analysis, the “20/20” definition provided a sensitive and specific rate of NCD. Ultimately, a larger sample size including both sexes and a larger age range coupled with a nonsurgical control group may provide a better assessment of what defines significant neurocognitive injury. Third, we did not determine whether there is any long-term benefit, although 1 of the predictors of neurocognitive dysfunction at 5 years is its presence at discharge. Undoubtedly, further follow-up, including a quality of life assessment and cost comparison, is important. Fourth, all patients recruited were male. Female patients less than 75 years of age receiving elective CABG surgeries are a minority of cases at our center. Although no gender differences with regard to rHuEpo have been demonstrated, such an effect cannot be excluded. Fifth, if correction for multiple comparisons had been made, the results would be less significant. Last, we selected our population to exclude potential confounders of neurocognitive testing. Our patients were not at high risk for postoperative complications, and caution should be applied to extrapolating our observations to high risk surgeries.

Summary

This study of rHuEpo as a neuroprotectant in patients undergoing CABG surgery is feasible and safe. The use of rHuEpo was associated with a trend in the reduction of NCD at 2 months. These data suggest a larger multicenter study of rHuEpo for neuroprotection in CABG surgery is realistic, practical, and warranted.

Sources of Funding

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Disclosures

Only the Department of Critical Care Medicine and the Division of Cardiac Surgery, University of Calgary and Calgary Health Region, reviewed the design and conduct of the study to supervise the involvement of an academic trainee. Design, conduct, collection, management, analysis, and interpretation of the data as well as preparation, review, and approval of the manuscript was independent from Ortho-Biotech Canada. Dr Gregory Haljan had full access to all the data in the study and takes responsibility for the integrity of the data and Dr Gregory Haljan and Dr David Zygun take responsibility for the accuracy of the data analysis.

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The Erythropoietin NeuroProtective Effect: Assessment in CABG Surgery (TENPEAKS): A Randomized, Double-Blind, Placebo Controlled, Proof-of-Concept Clinical Trial
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