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A DOUBLE-BLIND, PHASE II, PLACEBO-CONTROLLED STUDY TO DETERMINE THE SAFETY AND EFFICACY OF r-HuEPO IN REDUCING TRANSFUSION REQUIREMENTS IN PATIENTS UNDERGOING TOTAL HIP JOINT REPLACEMENT SURGERY (PROTOCOL NO. CR005887)

SYNOPSIS

PRINCIPAL INVESTIGATORS:
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STUDY DATES: March 9, 1990 - December 20, 1991

OBJECTIVES:
This study was designed to determine if recombinant human erythropoietin (r-HuEPO) given subcutaneously before and after surgery could prevent significant anemia and decrease the need for blood transfusion in patients undergoing elective total hip joint replacement surgery without adverse events when compared to placebo. The effectiveness of initiation of treatment with r-HuEPO 10 days vs. five days prior to surgery in reducing the occurrence of significant anemia and the need for blood transfusion was also compared.

STUDY DESIGN:
This was a Phase II, randomized, double-blind, placebo-controlled, multicenter study of r-HuEPO therapy in healthy adult patients undergoing total hip surgery, either a primary or revision hip replacement. The study was conducted at five sites (London, Ontario; Toronto, Ontario; Vancouver, British Columbia; Halifax, Nova Scotia; and Montreal, Quebec). The primary efficacy variable was defined as whether or not patients had a transfusion in the perioperative period or had a hemoglobin of less than 80 g/L. Transfusion of asymptomatic patients with a hemoglobin level of >90 g/L was discouraged during the trial; it was generally agreed that patients with a hemoglobin <80 g/L would be transfused.

A study flow chart is provided in Table 1. Each patient was to receive oral iron supplementation with 300 mg of ferrous sulfate (or parenteral equivalent) three times per day for three weeks prior to surgery (but one 300 mg tablet on first day and two 300 mg tablets on second day), continuing through one week after surgery.

* Overseeing investigator; did not enroll patients.

Table 1: Flow Chart of Study Procedures (Protocol CR005887)

		Preoperative Period (Day)											Postoperative Period (Day)								
Procedure	Within 10 Days of Iron Suppl[a]	1	2	3	4	5	6	7	8	9	10	Day of Surgery 11	1	2	3	4	5	6	7	Day of Discharge	3 Weeks After Surgery
Selection criteria	X																				
Medical history	X																				
Physical examination	X																				
Routine hematology	X								X		X		X		X		X		X	X	X
Serum biochemistry	X										X									X	
Serum iron, TIBC, serum ferritin	X										X									X	
Urinalysis	X										X									X	
Serum β HCG (if applicable)	X																			X	
Serum for EPO level	X																				
Serum for EPO antibody level	X																				X
Obtain body weight	X																				
Vital signs and adverse events recorded		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X[b]	X[b]	X[b]	X	X
Study drug administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Anticoagulant therapy													X	X	X	X	X	X	X		
Visual analog scales to assess pain, shortness of breath, and energy levels, and nursing acuity													X		X		X		X	X	
Venography																			X[c]		

[a] Iron supplementation: one 300 mg tablet, 21 days before surgery (Day -11); two tablets, Day -10; three tablets per day, Day -9 through postoperative Day 7.
[b] Adverse events only.

[c] Venography to occur on postoperative Day 7 or on the day of discharge if the patient left the hospital sooner.

SYNOPSIS (Continued)

Two hundred ten patients were to be equally randomized at Day 1 (10 days before surgery) to one of three treatment groups: Group I (placebo group) = placebo for ten days before surgery, on the day of surgery, and for three days after surgery; Group II (14-day r-HuEPO group) = 300 IU/kg r-HuEPO for ten days before surgery, on the day of surgery, and for three days after surgery; and Group III (9-day r-HuEPO group) = placebo for five days before surgery (Days 1 to 5) and 300 IU/kg r-HuEPO for five days before surgery (Days 6-10), on the day of surgery, and for three days after surgery. As a result of an interim analysis (65 patients) by an external committee (see below), the protocol was amended to enroll 212 patients in the ratio of 2:2:1 (Groups I:II:III, respectively). Patients were required to have their surgery within 48 hours of the scheduled date or were withdrawn from the study. All patients were required to receive low dose coumadin (sodium warfarin) as prophylaxis for deep vein thrombophlebitis for seven days after surgery. The external committee was to review the safety results after 70 and 140 patients had completed the study.

Efficacy was evaluated based on comparison of the proportion of patients who received perioperative homologous transfusions or who developed a hemoglobin level less than 80 g/L. However, emphasis was placed on the proportion of patients who actually received transfusions as the most clinically relevant. Secondary efficacy variables were: the total number of units transfused; the changes in erythroid variables (hemoglobin, hematocrit, and reticulocyte counts) and iron store variables (serum iron, ferritin, and TIBC) from the prestudy to presurgery period, from the presurgery period to Day 1 after surgery, and from Day 1 after surgery to discharge; nursing acuity; well-being assessments (pain, shortness of breath, and energy level); and the number of days in the hospital after surgery. Safety was evaluated on the basis of reported adverse events, number of lower limb deep venous thrombi, clinical laboratory tests, and vital signs measurements.

EXTERNAL SAFETY COMMITTEE:

Allan Donner, PhD, Professor and Chairman, Department of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario; Canada

Graham Pineo, MD, FRCPC, Hematologist and Chief, Department of Medicine, Calgary General Hospital, Professor of Medicine, University of Calgary, Calgary, Alberta; Canada

David E. Hastings, MD, FRCSC, Chief, Division of Orthopedic Surgery, Wellesley Hospital, and Professor of Surgery, University of Toronto, Toronto, Ontario; Canada

STUDY POPULATION:

Patients were to be of either sex, between the ages of 18 and 85 years, scheduled for elective unilateral surgical implantation of a total primary or revision hip prosthesis, with a baseline hemoglobin between 110 and 160 g/L, without significantly abnormal laboratory values for hematology and biochemistry which might indicate an impaired ability to respond to r-HuEPO, and able to understand and sign the consent form. The female patients were to be postmenopausal or protected from pregnancy by a reliable method of birth control.

A total of 208 (178 primary and 30 revision) patients were enrolled in the study; 78 patients were randomly assigned to the placebo-treated group, 53 to the 9-day r-HuEPO-treated group, and 77 to the 14-day r-HuEPO-treated group. Of these, 50% were male, 50% were female, the mean age was 63.3 years (range, 19.2 to 85.6 years), and the mean baseline hemoglobin level was 137.3±12.1 g/L. Of the 208 patients enrolled, 10 patients missed study medication and three patients had a second surgical procedure; thus 195 patients (166 primary and 29 revision) were evaluable for efficacy. Three patients were withdrawn from the study; one withdrew for protocol violation (intolerance to iron, 14-day r-HuEPO-treated group), one for adverse event (vasovagal response, 9-day r-HuEPO-treated group), one for other reasons (second surgical procedure, 9-day r-HuEPO-treated group).

EFFICACY RESULTS:

Of the patients evaluable for efficacy, 31 (42%) placebo-treated patients, 14 (29%) 9-day r-HuEPO-treated patients, and 17 (24%) 14-day r-HuEPO-treated patients required a transfusion; these data are summarized in Table 2. Because of a significant interaction between treatment and type of hip surgery (p=0.002), the two types of surgery (primary and revision) were looked at separately. For primary hip surgery patients, significantly fewer patients in the two r-HuEPO groups required transfusions (overall p=0.009, placebo vs 9-day r-HuEPO group p=0.018, placebo vs. 14-day r-HuEPO group p=0.011). For revision hip surgery patients, similar efficacy was not observed, but the number of patients was small. Similar results were observed for all patients (i.e., intent-to-treat analysis).

Table 2: Number (Percent) of Patients Requiring Transfusions, by Treatment (Protocol CR005887)

	Placebo	9 Days r-HuEPO	14 Days r-HuEPO
Patients Evaluable For Efficacy			
All evaluable patients[a]	(N=74) 31 (42%)	(N=49) 14 (29%)	(N=72) 17 (24%)
Primary hip surgery patients[b]	(N=63) 26 (41%)	(N=42) 8 (19%)	(N=61) 12 (20%)
Revision hip surgery patients[c]	(N=11) 5 (45%)	(N=7) 6 (86%)	(N=11) 5 (45%)
Intent-To-Treat Patients			
All patients[a]	(N=78) 34 (44%)	(N=53) 16 (30%)	(N=77) 18 (23%)
Primary hip surgery patients[d]	(N=67) 29 (43%)	(N=45) 9 (20%)	(N=66) 13 (20%)
Revision hip surgery patients[c]	(N=11) 5 (45%)	(N=8) 7 (88%)	(N=11) 5 (45%)

[a]Treatment by type of hip surgery interaction, p=0.002, using a loglinear model with treatment and type of hip surgery as factors.
[b]Overall, p=0.009; placebo vs. 9-day r-HuEPO, p=0.018*; placebo vs. 14-day r-HuEPO, p=0.011*; 9-day r-HuEPO vs. 14-day r-HuEPO, p=0.756.
[c]Number of patients was too small to determine statistical significance.
[d]Overall, p=0.004; placebo vs. 9-day r-HuEPO, p=0.012*; placebo vs. 14-day r-HuEPO, p=0.004*; 9-day r-HuEPO vs. 14-day r-HuEPO, p=0.942.

Note: *=statistically significant (using Bonferroni-Holm procedure).

Most patients (evaluable for efficacy) requiring transfusion received only one or two units of packed red cells (71% patients in each treatment group). As summarized in Table 3, for patients evaluable for efficacy, fewer mean units were transfused in each of the two r-HuEPO-treated groups; 0.97 units were transfused in the placebo group, 0.69 units in the 9-day r-HuEPO group, and 0.53 units in the 14-day r-HuEPO group, a reduction of almost 50% for the 14-day therapy. Because of a significant treatment by center by type of hip surgery three-way interaction, primary and revision hip surgery patients were again looked at separately. For primary hip surgery patients, significantly fewer units of blood were transfused in the two r-HuEPO groups (overall, p=0.005; 9-day vs. placebo, p=0.007; 14-day vs. placebo, p=0.004). For revision hip surgery patients, similar efficacy was not observed, but the number of patients was small. Similar results were observed for all patients (i.e., intent-to-treat analysis).

Table 3: Total Number of Units Transfused (Mean ± SD), by Treatment (Protocol CR005887)

	Placebo	9 Days r-HuEPO	14 Days r-HuEPO
Patients Evaluable For Efficacy			
All evaluable patients[a]	(N=74) 0.97 ± 1.34	(N=49) 0.69 ± 1.25	(N=72) 0.53 ± 1.16
Primary hip surgery patients[b]	(N=63) 0.87 ± 1.17	(N=42) 0.36 ± 0.76	(N=61) 0.36 ± 0.84
Revision hip surgery patients[c]	(N=11) 1.55 ± 2.07	(N=7) 2.71 ± 1.70	(N=11) 1.45 ± 2.07
Intent-To-Treat Patients			
All patients[d]	(N=78) 1.14 ± 1.70	(N=53) 0.70 ±1.22	(N=77) 0.52 ± 1.14
Primary hip surgery patients[e]	(N=67) 1.07 ± 1.64	(N=45) 0.36 ±0.74	(N=66) 0.36 ± 0.83
Revision hip surgery patients[c]	(N=11) 1.55 ± 2.07	(N=8) 2.63 ± 1.60	(N=11) 1.45 ± 2.07

[a]Treatment by center by type of hip surgery three-way interaction: p=0.003.
[b]Overall, p=0.005; placebo vs. 9-day r-HuEPO, p=0.007*; placebo vs. 14-day r-HuEPO, p=0.004*; 9-day r-HuEPO vs. 14-day r-HuEPO, p=0.887.
[c]Number of patients was too small to determine statistical significance.
[d]Treatment by center by type of hip surgery three-way interaction: p=0.015.
[e]Overall, p=0.001; placebo vs. 9-day r-HuEPO, p=0.002*; placebo vs. 14-day r-HuEPO, p=0.001*; 9-day r-HuEPO vs. 14-day r-HuEPO, p=0.979.

Note: *=statistically significant (using Bonferroni-Holm procedure).

For all evaluable patients, hemoglobin rose from baseline to presurgery by a mean of 9.1 g/L in the 14-day group and 2.2 g/L in the 9-day group while falling 2.7 g/L in the placebo group (overall, p<0.001). The degree of fall in hemoglobin as a result of surgery, from presurgery to postoperative Day 1, was least in the 14-day group (-27.2 g/L) compared to the 9-day group (-31.5 g/L) and the placebo group (-34.5 g/L); further analysis was performed because of a significant treatment by center by type of surgery interaction (p=0.007) revealing a significant difference between 14-day r-HuEPO-treated and placebo-treated primary hip surgery patients in this time period (p=0.001). Reticulocyte response was most vigorous in the 14-day r-HuEPO group from baseline to presurgery (overall, p<0.001). In both r-HuEPO-treated groups, r-HuEPO produced an early and sustained elevation in the serum reticulocyte counts. In the baseline to presurgery period, serum iron and serum ferritin values fell to a clinically significant extent in both 9- and 14-day r-HuEPO-treated groups. There were no statistically significant differences between the groups in measurement of nursing acuity and three measures of well-being in the postoperative recovery period.

SAFETY RESULTS:

Eight proximal (femoral vein) deep vein thrombophlebitides (three in 14-day and five in 9-day r-HuEPO-treated patients) were detected through both routine postoperative surveillance and spontaneous reporting in r-HuEPO-treated patients (p=0.026 placebo vs. r-HuEPO-treated groups combined). Thirteen distal (popliteal and calf veins) deep vein thrombophlebitides were discovered (five in placebo-treated, five in 14-day r-HuEPO-treated, and three in 9-day r-HuEPO-treated patients; p=1.000). Three of eight proximal and 11 of 13 distal thrombophlebitides were clinically asymptomatic. A summary of DVTs reported as adverse events (including all those detected by surveillance) is shown in Table 4.

Table 4: DVTs Reported as Adverse Events
(All Patients in Protocol CR005887)

	Placebo (N=78)	9-Day r-HuEPO (N=53)	14-Day r-HuEPO (N=77)	p values (1)	p values (2)
Proximal DVT	0 (0%)	5 (9%)	3 (4%)	0.016	0.026
symptomatic	0 (0%)	3 (6%)	2 (3%)	0.051	0.159
asymptomatic	0 (0%)	2 (4%)	1 (1%)	0.189	0.293
Distal DVT	5 (6%)	3 (6%)	5 (6%)	1.000	1.000
symptomatic	1 (1%)	1 (2%)	0 (0%)	0.721	1.000
asymptomatic	4 (5%)	2 (4%)	5 (6%)	0.860	1.000
Any DVT	5 (6%)	8 (15%)	8 (10%)	0.268	0.172

p values
(1) overall
(2) placebo vs. r-HuEPO (combined)

A summary of adverse events reported by more than 10% of the patients in any treatment group is shown in Table 5. The most common adverse event was skin reaction at the injection site, followed by pyrexia. Serious hypertension requiring the withholding of one to two doses of study medication occurred in three placebo-treated patients. One patient (14-day r-HuEPO-treated group) suffered a nonfatal myocardial infarction. There was one death; a placebo-treated patient suffered a brain stem infarct 14 days after surgery and died after having completed the study. One patient (9-day r-HuEPO-treated group) discontinued the study because of an adverse event (vasovagal response). IND safety reports were filed in Canada for 15 patients (placebo - one cholecystitis, one brain stem infarction/death; 9-day r-HuEPO - five thromboses, one each anaphylactic reaction, apneic spell, vasovagal attack; 14-day r-HuEPO - one myocardial infarct, four thromboses).

Table 5: Adverse Events Reported by ≥10% Patients in Any Treatment Group (All Patients in Protocol CR005887)

	Placebo (N = 78) No. (%)	9 Days r-HuEPO (N = 53) No. (%)	14 Days r-HuEPO (N = 77) No. (%)
Skin Reaction, Injection Site	50 (64%)	39 (74%)	57 (74%)
Burning	25 (32%)	23 (43%)	27 (35%)
Stinging	20 (26%)	14 (26%)	25 (32%)
Pain	9 (12%)	5 (9%)	12 (16%)
Pyrexia	33 (42%)	21 (40%)	28 (36%)
Thrombosis	5 (6%)	8 (15%)	8 (10%)
Nausea	5 (6%)	3 (6%)	11 (14%)
Diarrhea	3 (4%)	1 (2%)	10 (13%)
Dyspepsia	2 (3%)	6 (11%)	2 (3%)
Vomiting	0 (0%)	2 (4%)	8 (10%)

CONCLUSIONS:

Subcutaneous prophylactic administration of 300 IU/kg r-HuEPO for either five or 10 days before surgery, on the day of surgery, and for three days after surgery to a heterogeneous adult population of patients undergoing elective hip joint replacement surgery reduced the incidence of perioperative homologous red cell transfusions by 18% (42% vs. 24%) and 13% (42% vs. 29%) in the 14-day and 9-day r-HuEPO groups, respectively, as compared to placebo treatment. In the primary hip surgery patient population, both 14 days and nine days of treatment with r-HuEPO significantly reduced the risk of transfusion relative to placebo (overall, p=0.009) and significantly reduced the mean number of units of blood transfused relative to treatment with placebo (overall, p=0.005). Similar benefit was not observed among revision hip surgery patients, although the sample size was small. Significant increases in hemoglobin and reticulocyte counts between the baseline and presurgery period were observed for both r-HuEPO-treated groups compared with the placebo-treated group ($p<0.001$); the responses were significantly larger for the 14-day r-HuEPO-treated regimen than for the 9-day r-HuEPO-treated regimen. Hemoglobin levels were higher throughout the postoperative period in both r-HuEPO-treated groups than in the placebo-treated group; mean values reached the lower limit of normal by three weeks after surgery. In both r-HuEPO-treated groups, an earlier and sustained elevation in the serum reticulocyte counts was observed compared with the placebo-treated group. Daily oral iron supplementation, started three weeks before surgery, helped maintain normal serum iron and ferritin levels during the vigorous preoperative erythropoiesis. In the presence of routine, postoperative, low-dose coumadin prophylaxis against DVTs, there appeared to be a non-dose-related increase in ipsilateral proximal thrombophlebitis with r-HuEPO therapy. There was no statistically significant difference in the incidence of DVTs (proximal and distal combined). Subcutaneous injection of up to 300 IU/kg r-HuEPO daily for nine days or 14 days was well tolerated.

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