PROCRIT® (epoetin alfa)
Use of PROCRIT in Jehovah's Witnesses

SUMMARY

- Studies have been shown to demonstrate that epoetin alfa (EPO) has decreased the need for blood transfusions for Jehovah's Witness (JW) patients in the following clinical settings: cardiac surgery,[1-5] general surgery,[6, 7] liver transplantation,[8, 9] and autologous stem cell transplant.[10]
- Health-care professionals with questions about the use of PROCRIT therapy from a religious standpoint, may contact Hospital Information Services (United States) for Jehovah's Witnesses at jw.org/medical or via e-mail at hid.us@jw.org.

BACKGROUND

Formulation/Albumin Content

Albumin is added to each vial of PROCRIT to prevent adherence of the active ingredient, EPO, to the walls of the vial and other surfaces with which it comes into contact. The human albumin used in the formulation of PROCRIT is an aqueous solution obtained from large pools of adult human plasma. All plasma used to manufacture the human albumin used by the manufacturer of PROCRIT is regularly inspected by the Food and Drug Administration.

PROCRIT is not manufactured from human blood. Recombinant human erythropoietin is secreted by mammalian cells that have incorporated the human gene from erythropoietin into their own DNA. The cell line producing EPO for PROCRIT has been carefully characterized and does not carry transmissible microbial agents.

CLINICAL DATA

Cardiac Surgery

Prospective Studies

Podesta et al (2002)[1] evaluated the use of EPO and ferrous sulfate in anemic (hemoglobin [Hb] values between 9 and 11 g/dL) JW patients scheduled for elective heart surgery (N=45) who were expected to require ≥2 units (U) of blood transfusions.

Study Design

- Patients received EPO 10,000 IU (140 IU/kg) as a subcutaneous (SC) injection 3 times a week (TIW) during the 3 weeks prior to surgery, and ferrous sulfate 525 mg orally (PO) 3 times daily.

Results

- Prior to surgery, there was a significant increase in the hematocrit (Hct; ±13.7%) and Hb (±14.1%) when compared to baseline values. In the first 24 hours, there was 680 mL (±418) of blood loss.
- On average, patients were discharged and/or transferred to postheart surgery rehabilitation centers by postoperative day 5 (±3).
- On postoperative day 6, 1 patient was transferred to the intensive care unit due to hypoxemia that appeared after extubation on postoperative day 1.
- One patient who underwent a myocardial revascularization with an ejection fraction of 40% preoperatively, developed postoperative acute left ventricular failure and subsequently expired.

Rosengart et al (1997)[2] evaluated the use of EPO in adult JW patients undergoing open-heart surgery without transfusions (N=50).

Study Design

- Study included 3 groups:
  Group 1: thirty JW patients undergoing first-time coronary bypass;
  Group 2: thirty non-JW control patients undergoing first-time coronary bypass;
  Group 3: twenty JW patients undergoing more complex operations including reoperations and valve replacements with or without coronary bypass.
- Groups 1 and 3 participated in the multimodality blood conservation, while patients in group 2 participated in the "standard" blood conservation protocol.
- The multimodality approach included the following: high-dose EPO with an initial 300 U/kg intravenous (IV) bolus accompanied by a 500 U/kg SC injection, followed by 500 U/kg SC administered every other day (QOD) until surgery. EPO was continued until 3 days postoperatively or until patients reached a postoperative Hct ≥27%. Surgery did not occur until Hct reached 36% and calculated red blood cell (RBC) mass was sufficient to provide a minimum on-bypass Hct ≥18%. Iron sulfate (325 mg PO 4 times daily), vitamin C (500 mg PO twice daily), folate, and vitamin B_{12} were administered, as well as the intraoperative aprotinin Hammersmith regimen that included heparin. Other procedures were employed, including intraoperative autologous blood donation (IAD).
- In group 2 (control group), IAD consisted of withdrawal of 500 mL of blood immediately prior to cardiopulmonary bypass, which was reinfused after protamine administration. Intraoperative RBC scavenger techniques were also utilized. Transfusions of RBC were required at intraoperative Hct <16% and postoperative Hct count <22%.

Results

- Overall, 9 patients treated with EPO had their surgeries delayed and underwent extended preoperative EPO therapy on inpatient basis (15±6 days) due to an inadequate preoperative RBC mass (Hct: 29±4%; RBC mass: 1240±400 mL). After EPO therapy, Hct and RBC mass increased to 36±3% and 1750±430 mL, respectively. At discharge, patients had a Hct level of 32±4%.
- In group 2, 57% (n=17) of patients required homologous transfusions, 53% (n=16) required packed RBC transfusions, 10% (n=3) required platelets, and 13% (n=4) required fresh-frozen plasma. The mean total volume of homologous blood or blood products was 3.0±0.7 U and the mean amount of homologous blood per patient was 1.80±2.8 U.
- Preoperative Hct values for groups 1, 2, and 3 were 39±4%, 42±3% and 37±6%, respectively (groups 1 and 3 vs control; $P<0.05$). By the time of the operation, the Hct levels were not significantly different between group 1 JW patients and the control group.
- The mortality rate was 4%. Thromboembolic events were reported in 1 JW patient who developed a deep venous thrombosis after hospital discharge. One death and 1 stroke were reported in each group 1 and group 2. A myocardial infarction was reported for 1 patient in group 1 based on a new Q wave on an echocardiogram.
- One patient in both group 1 and group 2 developed renal insufficiency after surgery; 2 patients in group 1 had temporary creatinine increases >1 mg/dL.

Chikada et al (1996)[3] reported a study of JW patients who underwent open-heart surgery without the use of blood products (N=25). Five of these patients received EPO 6000 U IV QOD beginning 1 week prior to surgery and continued postoperatively until the Hct returned to preoperative level. Hematocrit increased by the day before surgery in all 5 patients that received EPO (mean baseline Hct: 37.2%; mean Hct prior to surgery: 43.2%). The lowest mean postoperative Hct was 27% (range, 16-36). Hematocrit gradually decreased until postoperative day 5, after which Hct increased. Patient 1 showed the greatest increase in Hct prior to surgery (baseline Hct: 29.6%; Hct prior to surgery: 41.7%) and received EPO 6000-18,000 U daily.

There was 1 death not related to blood loss. Due to excessive bleeding, 3 patients went back to surgery and no blood transfusions were given during additional operations.

Rosengart et al (1994)[4] evaluated the risk of requiring blood transfusions in patients (N=100) undergoing first-time coronary artery bypass grafting. Subsequently, a multimodality blood conservation program was developed based on these findings and the program was implemented in JW patients undergoing open heart surgery (N=15).

Study Design

- This was a prospective study combined with retrospective chart review.
- In the prospective study, the multimodality blood conservation program included intraoperative aprotinin administration (full Hammersmith regimen), EPO use, IAD, exclusive use of intraoperative cell salvage, continuous reinfusion of shed mediastinal blood, and low-prime cardiopulmonary bypass circuit.
    - EPO was started with an initial 300 U/kg IV bolus accompanied with a 500 U/kg SC injection followed by EPO 500 U/kg SC given QOD until the operation.
    - Surgery was delayed until a minimum Hct of 36%. EPO therapy was continued through postoperative day 5, or until discharge for patients with postoperative Hct <30%.
- The retrospective risk analysis did not identify risk advantage for blood loss or transfusion.
    - There were significantly fewer males in the JW group vs the control group (27% vs 73%; *P*<0.001).
    - The JW group had significantly less blood volume (4340±588 mL vs 5146±86 mL), Hct (37±3% vs 40±3%), and red cell mass (1610±260 mL vs 2050±440 mL) vs the control group (all *P*<0.001).
    - Hematocrit at the time of cardiopulmonary bypass and the lowest Hct during bypass were significantly lower for JW patients vs patients in the control group (both *P*<0.001). The first postoperative Hct and postoperative day 5 Hct were significantly higher for JW patients vs patients in the control group (*P*<0.01 and *P*<0.001, respectively).
    - Chest tube output was significantly lower for JW patients vs controls at 6 and 24 hours postoperatively (*P*<0.001).
    - One patient who underwent chronic dissection repair experienced a transient posterior circulation stroke manifested by cortical blindness. Two patients had a transient increase in creatinine levels of >1.0 mg/dL.

General Surgery

Prospective Follow-Up

Harwin et al (2012)[6] evaluated the experience of JW patients who underwent total hip arthroplasty revision without the use of blood products (N=10). Perioperative treatment included EPO 600 U/kg weekly x 3 weeks, iron 325 mg daily, and folate 1000 mg daily.

The mean follow-up was 69 months (range, 24-120 months). All patients were clinically well at most recent follow-up visit.

One patient had a deep vein thrombosis during the perioperative period and 1 patient had a superficial wound infection; both patients had recovered by follow-up.

Atabek et al (1995)[7] evaluated the use of EPO in JW patients with postoperative anemia (N=40). Twenty patients had Hct <25% and received EPO 300 U/kg IV TIW for 1 week followed by EPO 150 U/kg IV TIW for 2 additional weeks (n=13) and additional pre-protocol JW patients with severe postsurgery anemia had received EPO 100 U/kg IV TIW on a humanitarian basis (n=7; group E). Group C consisted of 20 control JW patients with severe anemia who did not receive EPO. All patients received IV and/or oral iron supplements (regimen unspecified).

All patients experienced some degree of acute blood loss during their procedure. At baseline, Hct was 15.8% in group E and 12.8% in group C (*P*=0.09). At week 1, Hct was

19.3% in group E and 12.5% in group C (P<0.0001). At week 2, Hct was 22.5% in group E and 17.8% in group C (P=0.09).

Three patients died in group E; 1 death occurred within the second week after starting EPO and 2 deaths occurring after completing 2 weeks of drug treatment. Four deaths occurred in group C, with 2 deaths occurring 2 weeks after EPO and 2 deaths occurring within the second week.

Liver Transplantation

Retrospective Studies

Jabbour et al (2005)[8] conducted a study to determine a methodology for orthotopic liver transplantation without transfusion (N=27). EPO 20,000 U SC twice weekly or 40,000 U once weekly was given preoperatively. If Hct reached 45%, EPO was held. Iron sulfate and folic acid supplementation (regimen unspecified) was given to all patients. All patients at induction underwent acute normovolemic hemodilution and received cell salvaging therapy.

There were 19 living donor (LD) transplants and 8 deceased donor (DD) liver transplants. All recipients survived in the LD group and 75% of patients survived in the DD group. Preoperative Hct was 42.8% (range: 34.9%-49.5%) in the LD group and 35.8% (range: 26.9%-45.3%) in the DD group. End of operation Hct was 37.8% (range: 23.5%-48.5%) in the LD group and 24.4% (range: 17.4%-34.8%) in the DD group. Discharge Hct was 32.7% (range: 21.1%-43.4%) in the LD group and 26.0% (range: 20.9%-33.9%) in the DD group.

Two patients from the DD group died: 1 died intraoperatively from primary graft nonfunction of the transplanted liver and the second patient died on the second postoperative day from severe anemia. All other patients survived after a mean follow up of 965 days in LD group and 624 days in the DD group with no additional bleeding complications reported.

Jabbour et al (2004)[9] developed strategies for transfusion-free live donor liver transplantation in JW patients (N=38). Patients were classified into 2 groups: the transfusion-free group (JW; n=8) and the transfusion-eligible group (non JW; n=30). The transfusion-free group received preoperative blood augmentation including EPO, iron sulfate, and folic acid, underwent intraoperative cell salvage, and acute normovolemic hemodilution. Transfusion-eligible patients received blood augmentation, intraoperative cell salvage, and acute normovolemic hemodilution in 7%, 80%, and 10%, respectively.

The mean total dose of EPO used per patient was 180,000 U (0-1,808,000 U) over a median of time of 21 days (0-226 days). The transfusion-free group had significantly higher mean Hct levels compared to the transfusion-eligible group due to preoperative EPO use (43.8±4.6 vs 35.3±5.3; P=0.0013). The mean stay in the intensive care unit and total hospital stay was 5±2.3 days (range 2-9 days) and 17.5±7.3 days (range, 8-27 days) in the transfusion-free group and 5.8±4.1 days (range, 2-18 days) and 19.5±13.3 days (range, 18-71 days) in the transfusion-eligible group, respectively. Patients in the transfusion-free group did not receive blood, fresh frozen plasma, or platelet transfusions; however, 80% of transfusion-eligible patients received a median of 4.5±3.5 units of packed RBCs. Patient survival was 100% in the transfusion free patients and 90% in the transfusion eligible patients (P=1.00).

Autologous Stem Cell Transplant

Ford et al (2015)[10] evaluated the experience of JW patients undergoing autologous stem-cell transplant without transfusions (N=125). Patients diagnosed with lymphoma (n=55), multiple myeloma (n=68), and amyloidosis (n=2) undergoing high-dose chemotherapy were included. Hemoglobin level of ≥ 11 g/dL and platelet level of ≥ 100 $x10^3/\mu L$ were required to start pre-transplant regimen consisting of daily IV iron, erythropoietin 60,000 U weekly, and cytokine mobilization of stem-cells. During post-transplant, patients received a 4-drug

combination of granulocyte colony-stimulating factor, erythropoietin, aminocaproic acid, and phytonadione. A total of 15 patients (83.3%) experienced Grade 1 bleeding complications and 4 patients (22%) experienced Grade 2-4 bleeding events. Cardiac complications were observed in 40 patients (32%) and 6 treatment-related deaths were reported. The following median values were reported: decrease in hemoglobin 5 g/dL, hemoglobin nadir of 7 g/dL, number of days with platelet count less than 100 x 10^3/µL 3 days, and mean platelet nadir of 5 x 10^3/µL.

LITERATURE SEARCH

A literature search of Ovid MEDLINE®, Embase, BIOSIS Previews®, and Derwent Drug File databases (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 13 July 2023. Retrospective studies, case series, and case reports describing the use of erythropoietin in JW patients have been published in the following clinical settings: anemia of prematurity,[11, 12] cardiac surgery,[13-32] other types of surgeries,[33-42] during hip arthroplasties,[43, 44] in hemolytic anemia,[45] in the intensive care setting,[46-51] in liver transplant,[52,53] hematology/oncology[54-65], in trauma and burns,[66-69] in gynecology,[70-72] and gastroenterology.[73-75] Other relevant studies identified include case reports and older literature.[4, 30, 76-120]

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