A multicenter randomized controlled trial of transfusion goals in elderly anemic patients with ischemic cardiac disease

Fay Lin

A. Background

Red cell transfusions for elderly patients with acute coronary syndromes are frequently given at a higher threshold, although there is insufficient evidence to support practice as standard of care. Transfusions are used to augment the delivery of oxygen to ischemic tissue. The benefit must be balanced against the risks of the microcirculatory, volume-related and inflammatory complications of transfusion in patients with ongoing cardiac ischemia.

A lower transfusion threshold of a hemoglobin of 7 rather than 9 had a protective effect in The Canadian Critical Care Trials Group multi-center RCT of transfusion requirements among medical intensive care patients.[1] In a prespecified subgroup analysis there was a nonsignificant trend toward higher mortality at the lower transfusion threshold among the elderly and patients with ischemic cardiac disease. Subsequently, a large observational cohort of Medicare beneficiaries 65 or older hospitalized with acute myocardial infarction demonstrated a graded relationship of transfusion with mortality with progressively lower admission hematocrit, with benefit in adjusted analysis below a 2 hematocrit of 30-33.[2]

If the mortality benefit observed in the Medicare cohort were a true estimate, then transfusion has such a large mortality benefit that it should be established as a standard of care. Interpretation of this data is hampered by unmeasured confounders, such as differential use of medical and interventional therapy for MI at different levels of anemia, and the unclear temporal relationship between admission hematocrit and later transfusion during hospitalization for myocardial infarction. The most recent Cochrane review of transfusion threshold found little data of sufficient methodologic quality to guide transfusion and urged further large clinical trials, particularly in patients with cardiac disease.[3] I propose a multi-center, randomized controlled trial of a liberal versus restrictive transfusion strategy in elderly patients with anemia and ischemic cardiac disease.

B. Study question

In elderly patients with anemia and unstable ischemic cardiac disease, is there a significant difference in mortality and morbidity between a liberal and restrictive transfusion strategy9

C. Patient population

Consecutive patients age >65 with myocardial infarction or an acute coronary syndrome at 20 hospitals will be screened over a period of 2 years. Patients will be eligible if they have a hematocrit of 33 or less. Patients will be excluded for active GI bleeding, active bleeding as defined by a drop in

[1] Hebert PC, Wells G, BlaJ chman MA et al. A Multicenter, randomized , controlled clinical trial of transfusion requirements in critical care. NEJM 1999 340: 409-417

[2] 2Wu Wen-Chih, Rathore SS, Wang Y et al. Blood transftision in elderly patients with acute myocardial infarction. NEJM 2001345:1230

[3] Hill SR, Carless PA, Henry DA, Carson JL, Hebert PC, McClelland DBL, Henderson KM. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

hematocrit of 10% over the 12 hours prior to enrollment, admission for cardiac surgery, an inability to receive blood products, brain death or imminent death within 24 hours, a DNR order, or inability to consent. Patients with chronic anemia or who develop cardiac ischemia while hospitalized for other reasons will not be excluded.

It is expected that approximately 1000 patients per institution per year will fulfill screening criteria, of which 10% have a hematocrit of 33 or less, and of which 50% will agree to enrollment, with accrual of 50 patients per institution per year. Women and minorities will be enrolled proportionate to the population distribution among the elderly. A Spanish speaking research coordinator will particularly assist with enrollment among Hispanics.

D. Study design and treatment protocols

Patients will be randomly assigned to one of two treatment groups, stratified according to center and to the class of cardiac ischemia identified at baseline (acute coronary syndrome without ST-T changes and negative troponin, acute coronary syndrome with ST-T changes or positive troponin, and ST elevation MI), and balanced with the use of permuted blocks of four or six. Sealed, opaque envelopes arranged in a computer generated random order will be prepared by the coordinating center and distributed to each participating institution, where they will opened sequentially to determine treatment assignments, with regular audit by the data, safety and monitoring committee.

All enrolled patients will begin protocolized admission orders with the standard of care for cardiac ischemia based on the class of cardiac ischemi4 identified at baseline, including aspirin, a statin, a beta-blocker, nitrates, oxygen, morphine, serial troponins, and EKGs for all patients unless contraindicated, and heparin, clopidogrel, a GPITbIIIa inhibitor, and thrombolysis or cardiac catheterization as appropriate and available at each institution. Physicians will be instructed to begin these protocolized admission orders upon enrollment before randomization.

The transfusion goal for the liberal-strategy group will be a 30-33% hematocrit, as suggested by the Medicare cohort. The transfusion goal for the restrictive-strategy group will be a 24-27% hematocrit, given the trend toward harm at a hemoglobin of 7g/dl in the ischemic cardiac disease subgroup. For seven days after enrollment, each group will be monitored by daily hernatocrit measurements and receive packed red blood cells as needed to reach the assigned transfusion goal. Physicians caring for the patients will be instructed to administer transfusions, one unit at a time, and to measure post-transfusion hematocrits. Patients may have hernatocrits greater than the transfusion goal spontaneously, but not by transfusion. Physicians will be instructed to administer additional fluids or diuretics to maintain euvolemia regardless of treatment group, and to call the coordinating center as needed for advice when a transfusion was not indicated by the study protocol.

All other management decisions are left to the discretion of the patients' physicians. Adherence to the transfusion protocol is required only during the first seven days. Compliance with the study protocol will be assessed with the daily hernatocrit measurement in each patient and transfusion records at weekly intervals, and feedback provided to patient physicians from the research nurse. It is not possible to blind patients or physicians to the group assignment.

E. Baseline assessment and data collection

At the time of randomization, demographic, diagnostic and therapeutic information will be collected, as well the class of cardiac ischernia, Killip class, past heart failure and past cardiovascular history. Once enrolled, the hernatocrit, troponin, use of red-cell transfusions, medications and cardiovascular interventions, resolution or recurrence of chest pain as documented in the chart, and EKG as documented in the chart will be recorded on a daily basis for seven days.

Lengths of stay in the hospital and occurrence of rehospitalization will also be recorded. After 30 days and 60 days, patients, family or health care facility contacts will be contacted for vital status. Patients, or their last known physician if patients are unavailable, will be surveyed by phone or in person

at 60 days for symptoms and new diagnoses using a checklist and structured interview. Based on collected symptom, laboratory and EKG data, the initial cardiac diagnosis and episodes of recurrent ischemia will be reviewed and categorized by three cardiologists at the coordinating center blinded to the treatment assignment, and disagreements resolved by consensus.

F. Outcome measures

The primary outcome will be death from all causes or recurrent ischemia in the 30 days after randomization. The secondary outcome will be a composite measure of all-cause mortality, recurrent ischemia, rehospitalization, or new-onset heart failure using the Framingham criteria from patient interview at 60 days. Other secondary outcomes include all-cause mortality alone, the mean hematocrit and transfusion requirement, the peak troponin, and the length of stay.

G. Power

Since this is a equivalency trial, we estimated the number of patients necessary for the study to have the power to rule out clinically meaningful differences in outcomes. We estimate that 450 patients per group will be needed to rule out an 10% difference in the 30-day combined endpoint with 80% power at the 5% significance level adjusted for one interim analysis. This assumes an overall mortality rate of 35%, as observed in the Medicare cohort, and an additional rate of recurrent ischemia of 10%, conservatively estimated at 30% of the mortality rate, for an overall combined event rate of 45%. We also assume a 1% rate of loss to follow-up and a 4% rate of crossover to the liberal strategy and I% crossover to the restrictive strategy, as seen in the CCCT trial.

H. Statistical analysis

The interventions will be compared on an intention-to-treat basis. Baseline variables and the rate of the primary combined outcome will be compared with use of Fisher's exact test. Kaplan-Meier survival curves for each group will be compared with use of a logrank test statistic. A logistic regression will be performed where expected confounders, including age, study center, class of cardiac ischemia, and history of heart failure are forced into the model. A second logistic regression will be performed using a forward, stepwise procedure to adjust raw mortality data with covariates found to significantly outcomes at a p<=O. 1. A priori subgroup analyses include patients in different classes of cardiac ischemia and history of heart failure.

Comparisons of hematocrit concentrations over time will be made using ANOVA with repeated measures. Comparison of length of stay will be made using the Wilcoxon ranksum test for independent samples.

I. Data, safety and monitoring

Coordinating center nurses and physicians will make themselves available by phone to physicians and patients at participating centers for advice regarding medication and fluid management when transfusions are not indicated, and documenting the reason for withdrawal from the study should patients or physicians so choose.

The data, safety and monitoring committee, consisting of a statistician, physician and nurse not otherwise involved in the study, will meet once every three months. They will monitor enrollment, quality of data collection, and compliance with study protocols, both for treatment group assignment and cardiac interventions, at each study center, and provide feedback. They will also review adverse events as documented by the study nurses and physicians.

One blinded interim analysis is planned at 1 year. The trial will be terminated early for a 20% difference in the combined endpoint between treatment groups.

J. Risks, benefits and inducements

There is no clear evidence to support a greater risk of mortality or morbidity at either transfusion goal. Benefits to participants include protocolized cardiac orders to ensure that patients have an acceptable standard of care. This is a nontrivial benefit, as in the Medicare cohort only 77% received aspirin and only 44% received a beta blocker on admission. In addition, cardiac patient education materials after discharge will be sent to home addresses of those who survive initial hospitalization. At the end of the study, participants or their families will receive letters from the coordinating center reviewing their treatment assignment, outcome, and results of the study. There are no monetary inducements for participation.