Conservative Versus Liberal Red Cell Transfusion in Acute Myocardial Infarction (the CRIT Randomized Pilot Study)

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Red blood cell transfusion is common in patients with acute myocardial infarction (AMI). However, observational data suggest that this practice may be associated with worse clinical outcomes and data from clinical trials are lacking in this population. We conducted a prospective multicenter randomized pilot trial in which 45 patients with AMI and a hematocrit level ≤30% were randomized to a liberal (transfuse when hematocrit <30% to maintain 30% to 33%) or a conservative (transfuse when hematocrit <24% to maintain 24% to 27%) transfusion strategy. Baseline hematocrit was similar in those in the liberal and conservative arms (26.9% vs 27.5%, p = 0.4). Average daily hematocrits were 30.6% in the liberal arm and 27.9% in the conservative arm, a difference of 2.7% (p <0.001). More patients in the liberal arm than in the conservative arm were transfused (100% vs 54%, p <0.001) and the average number of units transfused per patient tended to be higher in the liberal arm than in the conservative arm (2.5 vs 1.6, p = 0.07). The primary clinical safety measurement of in-hospital death, recurrent MI, or new or worsening congestive heart failure occurred in 8 patients in the liberal arm and 3 in the conservative arm (38% vs 13%, p = 0.046). In conclusion, compared to a conservative transfusion strategy, treating anemic patients with AMI according to a liberal transfusion strategy results in more patients receiving transfusions and higher hematocrit levels. However, this may be associated with worse clinical outcomes. A large-scale definitive trial addressing this issue is urgently required. **(Am J Cardiol 2011;108:1108–1111)**

In patients presenting with acute coronary syndromes (ACS) red blood cell (RBC) transfusion is a common yet highly variable practice with uncertain benefit.[1–5] We conducted a randomized pilot trial in which anemic patients with acute myocardial infarction (AMI) were randomly assigned to a traditional liberal transfusion strategy or a more conservative transfusion strategy. The purpose of this study was to assess the effect of this randomization scheme on RBC usage rates, hematocrit levels, and clinical safety in a preliminary manner and thus to inform the design of a definitive large-scale trial.

Methods

This was a prospective multicenter parallel-group randomized pilot trial to compare 2 RBC transfusion strategies in anemic patients with AMI. Patients were randomly assigned in a 1:1 ratio to 1 of 2 treatment groups by the coordinating center using consecutively numbered opaque envelopes. Blinding of treatment assignment was not feasible.

Patients admitted to the Washington Hospital Center, Washington, DC VA Medical Center, or Durham VA Medical Center with AMI from May 2003 through October 2009 were considered for enrollment. AMI was defined as ischemic-type chest discomfort lasting ≥30 minutes and associated with a creatine kinase-MB (CK-MB) or cardiac troponin level above the upper limit of normal (determined locally). We included patients in whom the hematocrit was ≤30% within 72 hours of symptom onset. We excluded patients for the following reasons: (1) noncoronary cause for clinical syndrome; (2) active bleeding, defined as overt blood loss accompanied by a decrease in hematocrit of ≥5% in the preceding 12 hours; (3) inability or unwillingness to receive RBC transfusion; (4) RBC transfusion within 7 days of enrollment; (5) previous severe transfusion reaction; (6) imminent death; (7) decision to provide limited or comfort care; (8) age <21 years; (9) pregnancy; (10) participation in another clinical trial in which RBC transfusion was a requirement or a component of a primary or secondary end point; and (11) previous participation in the present study.

The protocol was approved by the institutional review board of each participating institution. Written informed consent was provided by the patient or an appropriate surrogate. An independent data and safety monitoring board monitored the study and performed 4 interim safety analyses during the course of the study. The study was supported by the Cardiovascular Research Institute of the Washington Hospital Center and received no external funding (http://www.Clinicaltrials.gov, identifier NCT00126334).

Hematocrit was measured at least daily. Patients randomized to the liberal transfusion strategy underwent RBC transfusion when their hematocrit decreased <30% with the goal of maintaining a hematocrit from 30% to

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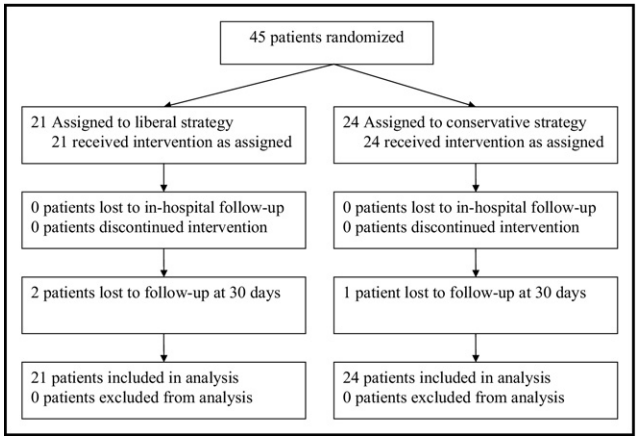

Figure 1. Participant flow diagram.

33%. Patients randomized to the conservative transfusion strategy underwent RBC transfusion when their hematocrit decreased <24% with the goal of maintaining a hematocrit from 24% to 27%. In the 2 groups leukocyte-depleted packed RBCs were transfused 1 U at a time and hematocrit was measured again 1 hour later. Additional units were transfused as necessary to achieve a hematocrit within the target range. If the hematocrit was >5% below the target range, 2 U were transfused before the hematocrit was measured again. If a patient underwent a major surgical procedure, RBCs were subsequently transfused according to the judgment of the treating physician until discharge from the hospital and any such transfusions were excluded from the transfusion-related analyses (other patient outcomes were not excluded).

Patients could receive RBC transfusion for any of the following reasons at the discretion of the treating physician: (1) active bleeding as defined earlier; (2) persistent hypotension related to hypovolemia; (3) active ischemia; and (4) at any time it was determined that it was in a patient's best interest to receive a transfusion. Once the active issue was resolved, transfusion was again administered according to the study protocol. In all cases patients were analyzed according to the randomization scheme ("intention to treat").

Transfusion-related end points included the proportion of patients receiving ≥1 transfusion, number of transfusions received per patient, and average daily hematocrit. The primary clinical safety measurement was a composite of the first occurrence of in-hospital death, recurrent MI, or new or worsening heart failure (HF). Each additional exploratory clinical end point reported below was prespecified.

Patients were followed daily by study personnel during their hospitalization and contacted by telephone at 30 days from randomization. Events were determined by the local study investigator. Recurrent MI was defined for nonprocedure-related events as recurrent ischemic chest discomfort, new ischemic electrocardiographic changes, and CK-MB increase above the upper limit of normal and increased by ≥50% over the previous value. For patients with percutaneous coronary intervention <24 hours previously, CK-MB ≥3 times the upper limit of normal and increased by ≥50% over the previous value was required. For patients with coronary artery bypass grafting surgery <24 hours previously, CK-MB ≥5 times the upper limit of normal and increased by ≥50% over the previous value was required. New or worsening HF was defined as 1 of the following occurring ≥6 hours after randomization: cardiogenic shock or a physician's decision to treat HF with an intravenous diuretic or intravenous vasoactive drug and evidence of pulmonary vascular congestion. Recurrent ischemia was

Table 1
Baseline characteristics according to transfusion strategy

Characteristic	Liberal (n = 21)	Conservative (n = 24)
Age (years), mean ± SD	76.4 ± 13.5	70.3 ± 14.3
Men	48%	54%
White	76%	61%
Smoker	10%	33%
Hypertension requiring drug treatment	91%	75%
Hyperlipidemia requiring drug treatment	76%	63%
Diabetes mellitus	81%	54%
End-stage renal disease	19%	17%
Previous coronary artery disease	52%	58%
Previous coronary artery bypass grafting	29%	17%
Previous percutaneous coronary intervention	24%	25%
Creatinine (mg/dl), mean ± SD	2.9 ± 2.3	2.4 ± 2.3
White blood cell count (1,000/μl), mean ± SD	9.4 ± 5.0	10.5 ± 3.8
Platelet count (1,000/μl), mean ± SD	201 ± 84	249 ± 100
Hematocrit (%), mean ± SD	26.9 ± 1.9	27.5 ± 2.4

Table 2
Myocardial infarction characteristics and treatments before randomization according to transfusion strategy

Characteristic	Liberal (n = 21)	Conservative (n = 24)
ST-segment elevation myocardial infarction	33%	46%
Non–ST-segment elevation myocardial infarction	67%	54%
ST-segment depression	43%	33%
Killip class		
I	52%	67%
II	24%	8%
III	0%	13%
IV	25%	13%
Ejection fraction (%), mean ± SD	47 ± 13	39 ± 15
Percutaneous coronary intervention	57%	54%
Fibrinolysis	5%	4%
Aspirin	100%	100%
Clopidogrel	81%	88%
Heparin	33%	41%
Glycoprotein IIb/IIIa inhibitor	5%	8%
β Blocker	62%	79%
Angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker	53%	63%
Nitrate	33%	21%
Diuretic	38%	13%
Statin	91%	92%
Intravenous vasoactive drug	29%	13%
Intra-aortic balloon pump	0%	13%
Mechanical ventilation	24%	13%
Pulmonary artery catheter	25%	25%

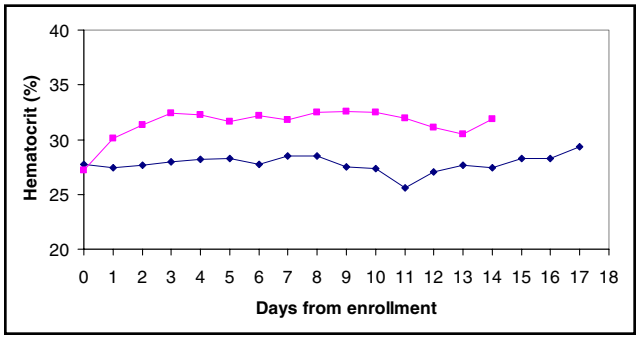

Figure 2. Average daily hematocrit according to a conservative *(diamonds)* or a liberal *(squares)* transfusion strategy.

defined as pain or discomfort considered probable or definite angina that was ≥5 minutes in duration.

The initial enrollment goal for the trial was 92 patients. After the fourth interim safety analysis, the data and safety monitoring board determined that an adequate number of patients had been enrolled to provide preliminary results with respect to transfusion-related end points and clinical safety. Therefore, in the face of slower-than-expected enrollment, the steering committee decided to halt further enrollment and the study was terminated after the last enrolled patient completed 30-day follow-up.

Between-group comparisons for continuous variables were made using *t* test or Wilcoxon rank-sum test and categorical variables were compared using a chi-square test or Fisher's exact test as appropriate. Curves of daily hematocrit values were compared using a mixed linear model. A p value <0.05 was considered to represent statistical significance. Because of the preliminary nature of this pilot study, no corrections were made for multiple comparisons.

Results

We enrolled 45 patients, of whom 21 were randomized to the liberal transfusion strategy and 24 were randomized to the conservative transfusion strategy (Figure 1). Mean time from AMI symptom onset to trial enrollment was 1.6 ± 0.5 days. Baseline characteristics are presented in Table 1 and were generally similar in the 2 treatment groups. MI characteristics and therapies at time of enrollment are presented in Table 2. There were 18 patients (40%) with ST-segment elevation MI and 27 patients (60%) with non–ST-segment elevation MI. Percutaneous coronary intervention had been performed in 25 patients (56%) before enrollment. Nearly all patients were receiving dual antiplatelet therapy.

Baseline hematocrit levels were similar in those randomized to the liberal and conservative treatment arms (26.9 ± 1.9% vs 27.5 ± 2.4%, p = 0.4). After randomization the mean hematocrit diverged in the 2 treatment arms and this difference was maintained throughout the study period (Figure 2). Average daily hematocrit levels were 30.6% in the liberal arm and 27.9% in the conservative arm, an absolute difference of 2.7% ($p<0.001$). More patients in the liberal arm than in the conservative arm were transfused with RBCs ≥1 U (100% vs 54%, $p<0.001$). Average number of units of RBCs transfused per patient trended higher in the liberal arm than in the conservative arm (2.5 ± 1.3 vs 1.6 ± 2.0, p = 0.07). Five patients in the conservative arm (21%) received a transfusion despite a hematocrit that was above the transfusion threshold. In 4 of these patients transfusion was administered in the setting of active bleeding as allowed by the protocol. One patient in each group erroneously received an RBC transfusion when the hematocrit was above the transfusion threshold. No transfusion reactions occurred.

Table 3
Clinical end points according to transfusion strategy

End Point	Liberal (n = 21)	Conservative (n = 24)	p Value
In-hospital death or recurrent myocardial infarction or new or worsening heart failure	38%	13%	0.046
In-hospital death	5%	8%	1.0
In-hospital death or recurrent myocardial infarction	5%	8%	1.0
In-hospital new or worsening heart failure	38%	8%	0.03
In-hospital recurrent ischemia	0%	4%	1.0
In-hospital death or recurrent myocardial infarction or new or worsening heart failure or recurrent ischemia	38%	17%	0.4
Coronary care unit length of stay (days), mean ± SD	3.4 ± 2.3	4.3 ± 3.3	0.3
Hospital length of stay (days), mean ± SD	8.5 ± 5.6	10.4 ± 7.2	0.3
Death at 30 days	5%	8%	1.0
Death or recurrent myocardial infarction at 30 days	10%	8%	1.0
Death or recurrent myocardial infarction or new or worsening heart failure at 30 days	60%	20%	0.02

In-hospital follow-up was complete for all patients. Three patients were lost to follow-up from hospital discharge to 30 days (2 in the liberal group and 1 in the conservative group). Clinical end points are presented in Table 3. The primary clinical safety measurement, a composite of in-hospital death, recurrent MI, or new or worsening HF, occurred in 8 patients in the liberal arm and 3 patients in the conservative arm (38% vs 13%, p = 0.046). Most of this difference was accounted for by an increase in the number of patients with new or worsening HF in the liberal arm (8 vs 2 patients). Recurrent ischemia occurred in 1 patient in the conservative arm and none in the liberal arm. Coronary care unit and hospital lengths of stay were similar in the 2 groups. At 30 days death, recurrent MI, or new or worsening HF occurred in 12 patients in the liberal arm and 4 patients in the conservative arm (60% vs 20%, p = 0.02). There were 2 deaths in the conservative arm (1 because of probable left ventricular rupture and 1 because of sepsis) and 1 in the liberal arm (because of progressive cardiogenic shock).

Discussion

This is the first report of a randomized trial comparing different RBC transfusion strategies in patients with AMI. In this small pilot trial we found that the randomization scheme we used was able to successfully maintain significantly different hematocrit levels at or near the target levels

for the 2 treatment groups throughout the study period. The conservative transfusion strategy was associated with a 36% relative decrease in the number of units transfused per patient and a 46% relative decrease in the proportion of patients receiving any transfusion. Furthermore, although our trial was not powered to detect differences in clinical outcomes, a significantly higher rate of adverse clinical outcomes—largely related to HF—was observed in patients randomized to the liberal transfusion strategy.

Theoretically, RBC transfusion might benefit patients with ACS by increasing oxygen delivery to ischemic myocardium but might be harmful by leading to transfusion reactions, transmission of diseases, circulatory overload, acute lung injury, and/or immunosuppression.[6] Previous studies of the role of RBC transfusion specifically in patients with ACS are observational and have shown conflicting results. Wu et al[5] found that RBC transfusion in Medicare beneficiaries with AMI was associated with a lower short-term mortality if the admission hematocrit was 30% and possibly ≤33%. In contrast, Rao et al[2] reported that RBC transfusion was associated with a higher 30-day mortality rate when administered to patients with ACS and a nadir hematocrit of ≥25%. Yang et al[1] reported a similar increase in mortality associated with RBC transfusion in patients with ACS enrolled in a large prospective registry.

To date randomized controlled trials in patients with ACS have been lacking. The Transfusion Requirements in Critical Care (TRICC) trial compared a restrictive RBC transfusion strategy (target hemoglobin 7.0 to 9.0 g/dl) to a liberal transfusion strategy (target hemoglobin 10.0 to 12.0 g/dl) in 838 anemic patients admitted to general intensive care units. Thirty-day mortality was similar in the 2 groups despite a 54% decrease in RBC transfusions in the restrictive strategy group.[7] In the subgroup with cardiovascular disease there was no significant difference in 30-day mortality. Results were not reported for patients with ACS.[8] The Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) investigators randomly assigned 2,016 high-risk elderly patients who were undergoing hip surgery to a liberal transfusion strategy (transfusion for hemoglobin <10 g/dl) or a symptom-driven transfusion strategy (transfusion for symptoms of anemia or if hemoglobin decreased to <8 g/dl).[9] Neither the primary functional end point nor the secondary cardiovascular end points were significantly different between treatment groups. The Transfusion Requirement After Cardiac Surgery (TRACS) trial randomized 502 patients undergoing cardiac surgery to transfusion triggers identical to those used in our study. The restrictive perioperative transfusion strategy resulted in noninferior rates of the combined outcome of 30-day mortality and severe morbidity.[6]

Our findings in patients with AMI, although clearly preliminary in nature, are in general agreement with these previous randomized trials in other patient populations in that we did not observe any signal of clinical harm in those patients randomized to a conservative transfusion strategy. Despite the small number of patients enrolled, the significantly lower rate of the primary clinical end point in the conservative transfusion group—driven by a decrease in HF events—is plausible because of the substantial volume load associated with RBC transfusion. It is reassuring that no patient in this group developed a recurrent MI and only 1 had recurrent ischemia.

Certain important limitations of our study must be acknowledged. First, despite the randomized design, there was imbalance between the randomized groups in some specific clinical characteristics. Second, a large proportion of patients in the 2 treatment arms underwent a revascularization procedure during their hospital stay. Risk of recurrent ischemia associated with a conservative RBC transfusion strategy might be greater in an AMI population treated with a less aggressive approach to revascularization. Third, the small number of patients enrolled in this study represents a minority of all patients with AMI admitted to the participating institutions during the time the study was ongoing. However, we believe our patients are representative of those patients with AMI and lower hematocrit values in whom RBC transfusion is often considered a therapeutic adjunct.

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