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Blood Transfusion After Myocardial Infarction: Friend, Foe or Double-Edged Sword? The CADILLAC study

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ABBREVIATIONS

AMI = acute myocardial infarction
CAD = coronary artery disease
PCI = percutaneous coronary intervention
RBC = red blood cell
STEMI = ST-segment elevation myocardial infarction

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ABSTRACT

Combined mechanical and pharmacological interventions constitute the cornerstone of therapy for patients with ST-segment elevation acute myocardial infarction (AMI). These increasingly complex interventions offer morbidity and mortality advantage but are associated frequently with bleeding complications. Major bleeding is probably the most important non-cardiac complication in patients undergoing coronary artery intervention. Prior studies have identified anemia as a strong independent predictor of mortality and adverse cardiac events in this patient population. Limited data are available to guide transfusion decisions in patients with coronary artery disease and anemia either at baseline or after a complication of an angioplasty procedure.

The CADILLAC study sought to determine the relationship between red blood cell transfusion and clinical outcomes in patients undergoing primary percutaneous coronary intervention for AMI. Out of 2,060 randomized patients, 82 (3.98%) received red blood cell transfusion during index hospitalization. Transfusion was independently associated with baseline anemia, older age, multivessel disease, and female gender. Patients transfused, versus patients not transfused, had significantly higher rates of one year mortality (23.9% vs. 3.4%), disabling stroke (2.5% vs. 0.5%), reinfarction (7.0% vs. 2.2%) and composite major adverse cardiac events (41.0% vs. 16.6%). After multivariable adjustment for potential confounders, red blood cell transfusion was independently associated with mortality at 30 days and one year (hazard ratio 4.71 and 3.16 respectively, both $p=0.0005$). The authors concluded that red blood cell transfusion after primary angioplasty in the setting of an AMI may be harmful or alternatively transfusion could be a marker of markedly increased risk, with further randomized studies needed to determine the optimal threshold for red blood cell transfusion in this patient population setting.

INTRODUCTION

Despite the widespread use of red blood cell (RBC) transfusions in patients with chronic anemia and active hemorrhage, there are limited data to guide transfusion decisions in patients with coronary artery disease (CAD). Additionally, improved survival in patients with CAD after RBC transfusion has not been demonstrated prospectively. Data from multiple series of patients with acute myocardial infarction (AMI) and transfusion varied possibly due to differences in the baseline hemoglobin levels as well as nadir hematocrit values after the procedure.^{1,2} In the large GUSTO

IIB trial (Global Use of Strategies To open Occluded coronary arteries) in which patients treated with only pharmacological reperfusion, blood transfusion was associated with a more than two fold increase in 30 day and one year mortality as well as increased rates of reinfarction.³ Similar results are available in patients undergoing percutaneous coronary intervention (PCI) and stable CAD disease, where blood transfusion was found an independent predictor of in-hospital and one year mortality.⁴ In a different setting, the landmark TRICC (Transfusion Requirement In Critical Care) randomized trial of critically ill patients found that a liberal transfusion strategy had no benefit, whereas a restrictive strategy of RBC transfusion was at list as effective and possibly a superior strategy in this population setting; however this could not be demonstrated for sure for patients with AMI or unstable angina.⁵

CADILLAC TRIAL

In the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial,⁶ a total of 2,082 patients of any age with AMI within 12 hours of symptom onset undergoing primary PCI in a native coronary artery eligible for stent implantation were randomized to one or four mechanical reperfusion strategies: coronary angioplasty (PTCA) with or without abciximab versus PTCA and stenting with Multilink stent with or without abciximab. The design, principal results, major inclusion and exclusion criteria, as well as dosage protocols have been reported previously. The original study evaluated clinical outcomes including death from any cause, reinfarction, target vessel revascularization as a result of ischemia and disabling stroke during index hospitalization, at 30 days and one year. In this particular study⁷ evaluating the prognostic impact of RBC transfusion after primary angioplasty for AMI, patients were stratified into three groups: 1) patients administered one or more units of RBC due to moderate or severe bleeding; 2) patients administered RBC transfusion in the absence of overt major bleeding; 3) patients who did not receive RBC transfusion. Patients who underwent coronary artery bypass surgery during hospitalization were excluded from present analysis. With respect to the statistical analysis, categorical variables were compared using the Fisher exact test, continuous variables were presented as medians with interquartile ranges and were compared using the non-parametric Kruskal-Wallis test. Clinical outcomes data were estimated by the Kaplan-Meier method and compared by log rank test. Multivariable analysis of predictors of mortality was performed using time-dependent Cox proportional hazards regression with stepwise selection using alpha entry and exit criteria of <0.10 and <0.15, respectively. A RBC transfusion was treated as a time-dependent covariate and entered the model along with all variables considered to be significant. To account for any confounding effect between transfusion

and clinical outcomes a propensity score for RBC transfusion was constructed and included in the multivariable model; its discrimination was assessed by the goodness of fit with the Hosmer-Lemeshow statistic, and its predicted performance was assessed with the C statistic.

During the index hospitalization of 2,060 randomized patients not treated with bypass surgery, 82 patients (3.98%) received RBC transfusion, including 33 patients (1.60%) in whom a transfusion was administered in the setting of moderate or severe bleeding and 49 patients (2.38%) who were transfused in the absence of moderate or severe bleeding. The RBC transfusions were administered to 75 out of 1,681 patients (4.5%) enrolled in the United States as compared with 7 out of 379 patient (1.8%) enrolled in other countries ($p=0.015$). One RBC unit was transfused in 8.5% of patients, two units in 54.9% patients and ≥ 3 units in 36.6% of patients.

Patients who received RBC transfusion were older, more frequently female, had a higher prevalence of prior gastrointestinal bleeding, chronic renal insufficiency, multivessel disease and lower body mass index. Baseline values of hemoglobin and hematocrit were lower and as such anemia at baseline was more frequent in patients received RBC transfusions. Time from AMI onset to the first balloon inflation was also longer in patients who received RBC transfusions. With respect to procedural characteristics longer procedure duration, lower post procedure TIMI flow grade, smaller post procedure reference vessel diameter and lower rates of procedural success were also associated with subsequent RBC transfusion. Administration of abciximab per randomization did not differ significantly between the two groups; however more patients in a transfusion group received abciximab for bailout indication.

Patients who received RBC transfusion associated with moderate or severe bleeding versus those without overt major bleeding versus those not transfused had significantly lower nadir hematocrit values. Patients receiving versus those not receiving RBC transfusion during index hospitalization had markedly higher rates of 30-day and one-year mortality, disabling stroke, reinfarction and composite major adverse cardiac events. Additionally, patients who received blood transfusion without associated moderate or severe bleeding tended to have higher rates of 30 days and one-year death, target vessel revascularization and composite major adverse cardiac events than did patients who received transfusions in the setting of clinically evident hemorrhage. After multivariable adjustment for potential confounders transfusion propensity, RBC transfusion was identified as an independent predictor of mortality at 30 days and one year.

DISCUSSION

The principal findings of the CADILLAC analysis which was the first such investigation examining the relationship

between blood transfusion and outcomes in patients undergoing primary PCI for AMI are the following: 1) RBC transfusion was administered to 3.9% of patients despite the absence of clinically overt moderate or severe bleeding in more than one half of these cases; 2) baseline anemia represented the strongest independent predictor of RBC transfusion; 3) patients received RBC transfusion had worse clinical and angiographic features at baseline, longer time from symptom onset to balloon inflation and PCI duration, worse procedural outcomes and larger infarct sizes; 4) after adjustment for potential confounders including baseline anemia and transfusion propensity, RBC transfusion but not anemia remained a powerful independent predictor of 30-day and one-year mortality; 5) the prognosis following RBC transfusion tended to be worse among patients without an associated moderate or severe hemorrhagic event than in those who were transfused due to clinically evident major bleeding. The nadir hematocrit values that triggered blood transfusion in the present analysis varied greatly with more than one half of patients receiving a blood transfusion with a nadir hematocrit value of greater than 30%. These observations reflect the lack of a uniform standard to guide the appropriateness of blood product usage. Of the total 4% of patients who received transfusions roughly one in four died and in two suffered an adverse cardiac event at one year.⁸ This is after excluding all the patients who had coronary artery bypass surgery. However the incidence of anemia and its associated transfusion were so closely related that the resulting interaction interfered with identification of the real culprit, but the transfusion propensity score was the key element to clear these data analysis.

Some issues, however, needed to be commented. First, the study provides a post hoc analysis of prospectively collected data within the context of large randomized trial. Transfusion was a post randomization event and the association between transfusion and outcomes has the potential of risk of bias due to unmeasured residual confounders. Additionally, the anemia cause was never established and that may have major prognostic implications. Finally, the potential effect of discontinuation of antithrombotic and antiplatelet medications due to bleeding was not investigated and may have contributed to a more adverse outcome.

In patients with AMI, *bleeding prevention* is of paramount importance. Multiple studies have shown that baseline anemia and transfusion were considered to be important predictors of adverse outcomes in patients artery doing PCI either in selective or emergency settings. Consequently, strategies that diminish bleeding risk while maintaining efficacy in reducing ischemic complications are very important. The role of newer anticoagulants, dose adjustments per gender, body mass index and baseline bleeding risk, meticulous puncture technique in the case of femoral approach or shifting to radial approach⁹

are some important attractive measures to diminish bleeding risk. More important, once prevention have failed a threshold for optimal transfusion should be defined. Transfusion may simply be a predictor of an outcome, the proverbial friend of a friend. Accumulate evidence strongly suggest that in patients with AMI transfusion may indeed become a real “*foe*”. Therefore, until more information is available a conservative approach with restrictive indications of blood products transfusion appears warranted. Widespread adoption of restrictive transfusion strategies might significantly improve clinical outcomes in this patient population, thus shifting this therapy into a trusting “*friend*”.

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