

Variations in the Use of Blood Transfusion in Patients with Coronary Artery Disease

Antonio Gutierrez, MD¹ and Sunil V Rao, MD, FACC, FSCAI²

1. House Officer, Department of Internal Medicine, Duke University Medical Center;

2. Assistant Professor of Medicine, Duke University Medical Center, and Director, Cardiac Catheterization Laboratories, Durham Veterans Affairs Medical Center

Abstract

Blood transfusions are frequently given to patients to treat low hemoglobin levels in the setting of non-ST-segment elevation acute coronary syndromes, percutaneous coronary intervention, and coronary artery bypass grafting. Evidence suggests that blood transfusion therapy in the setting of ischemic heart disease is associated with an increased risk for morbidity and mortality; however, there are no randomized clinical trials concerning transfusion strategies in ischemic heart disease. The evidence to date is observational and subject to confounding influences. This lack of definitive data has led to wide variations in transfusion practice in both the US and the international medical community. The purpose of this article is to examine the current literature concerning the transfusion practice of whole or packed red blood cells in the US and internationally in patients with ischemic heart disease. We propose that a prospective, randomized, controlled trial of transfusion strategies in ischemic heart disease is needed to determine the role of transfusion in this patient population.

Keywords

Anemia, hemoglobin, hematocrit, blood transfusion, ST-segment elevation acute coronary syndrome, non-ST-segment elevation acute coronary syndrome, coronary artery bypass grafting, percutaneous coronary intervention

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Correspondence: Antonio Gutierrez, MD, Box 31022/DUMC, Durham, NC 27710. E: antonio.gutierrez@duke.edu

Current evidence-based therapies for ischemic heart disease include antithrombotic and antiplatelet medications that reduce the risk for ischemic outcomes such as myocardial infarction and stroke.¹ Given their mechanism of action, bleeding is a risk with these agents, especially when combined with invasive procedures.² In addition to overt bleeding, clinical trials of antithrombotic strategies suggest that these patients also are subject to acute anemia (manifested as decreases in hemoglobin values during hospitalization) and blood transfusion. Several studies have shown a powerful association between anemia and adverse outcomes among patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS).³ A common strategy to deal with both bleeding and anemia in the ACS population is blood transfusion. Ostensibly given to increase hemoglobin levels and improve oxygen delivery to ischemic myocardial tissue, clinical and laboratory evidence suggests that blood transfusion not only does not improve oxygenation but also is associated with worse clinical outcomes. It is important to note that these data analyses are observational, retrospective, and subject to confounding influences.⁴ Indeed, there has never been a randomized trial of transfusion strategies in ischemic heart disease. This lack of definitive data has resulted in wide variation in transfusion practice. The purpose of this article is to summarize the current literature on the association between blood transfusion and outcomes and to review variations in transfusion practice in patients with ischemic heart disease.

Association Between Blood Transfusion and Outcomes

Recent retrospective studies have investigated the association between blood transfusion and outcomes in patients with NSTE ACS, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). Rao et al.⁵ examined 24,000 patients with NSTE ACS and found an association between blood transfusion and increased 30-day mortality (adjusted hazard ratio 3.94, 95% confidence interval [CI] 3.26–4.75). Similarly, Wu et al.⁶ found an association between transfusion and increased mortality among elderly Medicare beneficiaries with acute MI when transfusion was given for an admission hematocrit level above 33%. Mortality was lower with transfusion among patients with an admission hematocrit level <30%. Yang et al.⁷ examined the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) National Quality Improvement Initiative registry of ACS patients and found an association between transfusion and increased in-hospital mortality (adjusted odds ratio 1.67, 95% CI 1.48–1.88). Three studies have found an association between transfusion and adverse outcomes among patients undergoing PCI. Jani et al.⁸ found an association between blood transfusion and in-hospital mortality among patients

undergoing PCI within seven days of a myocardial infarction. Similarly, a registry study by Kinnaird et al.⁹ found that transfusion was associated with both in-hospital and one-year mortality among a broad sample of patients undergoing PCI. These adverse associations have also been shown in the setting of CABG. Murphy et al.¹⁰ reported that red blood cell transfusion was associated with higher risks for infection, ischemic post-operative morbidity, and increased 30-day mortality following cardiac surgery. These risks appear to be higher when transfused blood is more than two weeks old.¹¹

Although there is consistency across these studies in terms of the direction of the relationship between transfusion and outcomes (i.e. all of the studies suggest harm to a varying degree), all of the

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analyses were observational and subject to various confounding influences. Published transfusion guidelines do not recommend blood transfusion for patients who are stable regardless of the nadir hemoglobin value; however, specific guidelines are not available for patients with ischemic heart disease. Given this lack of guidance, studies demonstrate that there is wide variation in the use of blood transfusion among patients with NSTEMI ACS and those undergoing PCI and CABG.

Variation in Transfusion Practice

US Practice

Approximately 10–15% of patients with NSTEMI ACS undergo blood transfusion during an index hospitalization.⁷ The CRUSADE registry sampled 478 US hospitals and found that 30% transfused more than 20% of their NSTEMI ACS population and 15% transfused fewer than 5%. Patients who were admitted to larger teaching hospitals and did not have a cardiologist as their attending physician were more likely to undergo transfusion, with a median transfusion of two units. Among patient-level characteristics, renal insufficiency, older age (≥ 75 years), and presenting congestive heart failure were independent predictors of transfusion. As would be expected from the broad representation of patients enrolled in a registry, the transfusion rates in the CRUSADE initiative are higher than in NSTEMI ACS trial populations. Sabatine et al.³ reported a transfusion rate of 2.7% among NSTEMI ACS patients enrolled in a clinical trial, while Rao et al.⁵ reported a rate of 10% in a clinical trial population. In efforts to decipher the reasoning behind physicians' transfusion practices, Hebert et al.¹² surveyed critical care physicians in Canada and showed a preference for aggressive transfusion strategies to maintain a hematocrit level of 30% in patients with coronary artery disease.

To determine variation in transfusion practice among patients undergoing PCI, Moscucci et al.¹³ examined a single-center database and found that 8.9% of the study population received a blood transfusion after coronary intervention; transfusions were found to be more common in patients undergoing coronary stenting or placement of an intra-aortic balloon pump. The appropriateness of the transfusion was also studied using the American College of Physicians (ACP) transfusion guidelines.¹⁴ When these guidelines were applied, 76% of transfusions were deemed to be inappropriate.¹³ In a large study involving three centers, Kinnaird et al.⁹ examined the transfusion rate in 10,974 patients undergoing PCI and found that 5.4% of patients received a transfusion during hospitalization. A larger study by Jani et al.⁸ examined predictors for receiving blood transfusion after undergoing PCI among 17,177 patients within seven days of acute MI. In this study, 22.3% of patients with anemia received a post-PCI transfusion.

Patients undergoing CABG surgery are at high risk for bleeding and transfusion. However, there is also variation in transfusion practice in this high-risk group. A study of patients undergoing elective CABG at 18 tertiary care academic hospitals showed a significant variation in the mean number of units transfused per patient across centers. The percentage of patients receiving blood transfusion ranged from 17 to 100%. After controlling for patient and surgical practice variables, 'transfusion practice factors' accounted for variation in red blood cell transfusion rates rather than bleeding rates or patient comorbidities. In efforts to allow more rational resource allocation of whole and packed red blood cells, a study group examined the post-CABG transfusion practices of a large Canadian university hospital. The overall transfusion rate for all patients undergoing isolated CABG procedure was 23%, with 96.2% receiving packed red blood cells. Risk factors identified for blood transfusion in isolated CABG patients were a pre-operative hemoglobin of 12.07g/dl or less, emergent operation, renal failure, female gender, age greater than 70 years, ejection fraction less than 40%, redo procedures, and a body surface area less than 1.80m².

International Practice

Analysis of data from three large international randomized trials of patients with NSTEMI ACS revealed that non-US patients are significantly less likely to receive a transfusion for both non-invasive and invasive treatment (cardiac catheterization, PCI, and/or CABG). Thirty-day and six-month clinical outcomes in this patient population were similar across countries, suggesting that the aggressive use of transfusion among US patients did not translate into better outcomes. There are no data on international variation in transfusion practice among patients undergoing PCI or CABG outside of the NSTEMI ACS setting.

Future Directions

The evidence supporting blood transfusion to correct anemia in coronary artery disease is poor. A randomized trial of transfusion strategies is essential to guide clinical practice; however, until such a trial is performed, efforts should focus on preventing the use of transfusion therapy in this patient population. One effective strategy is improving patient risk stratification to prevent bleeding, thus negating the 'need' for transfusions. Identification of groups at high risk for bleeding complications should help guide selection of management strategies.

Studies that have focused on identifying risk factors for bleeding in STE ACS, NSTEMI ACS, and PCI have found that older age, females, lower bodyweight, the use of invasive procedures, and renal insufficiency are associated with bleeding complications.^{15,16} In an era where the mainstay of ACS therapy involves the use of multiple antithrombotic medications and invasive procedures in patients at high risk for subsequent ischemic events, it is essential to recognize that the elderly and those with renal insufficiency are at most risk for bleeding and are the subgroup most likely to benefit from therapies that reduce bleeding while maintaining an appropriate antithrombotic effect.^{2,17} Older, smaller patients have a lower creatinine clearance, which would explain why studies have revealed an increased risk for bleeding in this population when three or more antithrombotic agents are implemented.⁷

In order to prevent bleeding, the goal of antithrombotic and antiplatelet therapy during the treatment of ACS must be optimal ischemia reduction with simultaneous minimization of bleeding risk. Inappropriate dosing of antithrombotic and antiplatelet medications has been implicated as a cause of bleeding and is the primary reason behind the recommendation made by the guidelines advocating weight-based dosing of unfractionated heparin.^{18,19} Proper dosing of low-molecular-weight heparin and glycoprotein IIb/IIIa inhibitors based on creatinine clearance or glomerular filtration rate (GFR) is also essential. Studies have associated an exponential risk for bleeding in patients with a creatinine clearance <60ml/minute or GFR <60ml/minute/1.73m³ bodyweight.²⁰ Furthermore, the use of agents such as bivalirudin, a direct thrombin inhibitor, and fondaparinux, a synthetic pentasaccharide, is also associated with less bleeding,²¹ although a discussion of their risks and benefits is beyond the scope of this article.

Conclusions

The controversy over the appropriate role of blood transfusion in patients with ischemic heart disease has led to wide variation in transfusion practice, both within the US and worldwide. Studies have shown that a large proportion of transfusions given to patients with coronary artery disease are inappropriate, and that US patients are much more likely to receive blood despite having similar rates of anemia and bleeding to non-US study populations. This has not translated into better outcomes. Therefore, a randomized trial of transfusion strategies is needed to guide clinical practice. Until then, transfusion is probably best avoided whenever possible, and bleeding risk should be taken into account when triaging patients with ACS. ■



Antonio Gutierrez, MD, is a House Officer in the Department of Internal Medicine at Duke University Medical Center. His main research interests deal with clinical cardiology, critical care, and invasive cardiology. Dr Gutierrez has authored or co-authored numerous articles that have appeared in peer-reviewed journals.



Sunil V Rao, MD, FACC, FSCAI, is an Assistant Professor of Medicine at Duke University Medical Center and Director of the Cardiac Catheterization Laboratories at the Durham Veterans Affairs Medical Center. His main research interests deal with phase II clinical trials exploring pharmacological and interventional therapies for acute coronary syndromes, as well as bleeding and blood transfusion complications among patients with ischemic heart disease. Professor Rao is Associate Editor of the *American Heart Journal*.

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