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Hemoglobin Level and Hospital Mortality Among ICU Patients With Cardiac Disease Who Received Transfusions

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ABSTRACT

BACKGROUND There is a paucity of randomized clinical trial data on the use of red blood cell (RBC) transfusion in critically ill patients, specifically in the setting of cardiac disease.

OBJECTIVES This study examined how hemoglobin (Hgb) level and cardiac disease modify the relationship of RBC transfusion with hospital mortality. The aim was to estimate the Hgb level threshold below which transfusion would be associated with reduced hospital mortality.

METHODS We performed secondary data analyses of Veterans Affairs intensive care unit (ICU) episodes across 5 years. Logistic regression quantified the effect of transfusion on hospital mortality while adjusting for nadir Hgb level, demographic characteristics, admission information, comorbid conditions, and ICU admission diagnoses.

RESULTS Among 258,826 ICU episodes, 12.4% involved transfusions. Hospital death occurred in 11.6%. Without comorbid heart disease, transfusion was associated with decreased adjusted hospital mortality when Hgb was approximately <7.7 g/dl, but transfusion increased mortality above this Hgb level. Corresponding Hgb level thresholds were approximately 8.7 g/dl when comorbid heart disease was present and approximately 10 g/dl when the ICU admission diagnosis was acute myocardial infarction (AMI). Sensitivity analysis using additional adjustment for selected blood tests in a subgroup of 182,792 ICU episodes lowered these thresholds by approximately 1 g/dl.

CONCLUSIONS Transfusion of critically ill patients was associated with reduced hospital mortality when Hgb level was <8 to 9 g/dl in the presence of comorbid heart disease. This Hgb level threshold for transfusion was 9 to 10 g/dl when AMI was the ICU admission diagnosis. (J Am Coll Cardiol 2015;66:2510–8) © 2015 by the American College of Cardiology Foundation.

Hemoglobin (Hgb) level thresholds drive red blood cell (RBC) transfusion practices in critically ill patients, with additional influence exerted by other patient factors, such as increased age, severity of illness, gastrointestinal hemorrhage, comorbid heart disease, and acute myocardial infarction (AMI) (1–7). Over the past 2 decades, research has led to better understanding of the extent to which these transfusion thresholds influence mortality.

In the landmark TRICC (Transfusion Requirements in Critical Care) trial, patients randomly assigned to a restrictive strategy of receiving transfusions only when Hgb levels fell to <7 g/dl had significantly lower hospital mortality compared with a liberal strategy of transfusing when Hgb was <10 g/dl (2). Subsequent observational studies of intensive care unit (ICU) patients yielded mixed results, with some demonstrating increased mortality with transfusion, whereas others showed the opposite (4,5,8–12). Subgroups that derived greater benefit from transfusions included those with cardiac disease, such as those with severe ischemic heart disease (13) and AMI (14). These findings were by no means consistent across

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studies, with some showing benefit only when Hgb was <8 g/dl (12,15–18). In contrast, a recent, pilot randomized controlled trial (RCT) documented reduced mortality with a liberal transfusion strategy in the setting of acute coronary syndrome (ACS) or stable angina (19). For congestive heart failure (CHF), the impact of transfusion is even more uncertain (20). Notably, the American Association of Blood Banks clinical practice guidelines recommended a restrictive transfusion strategy for hospitalized patients with pre-existing cardiovascular disease for an Hgb level ≤8 g/dl, but these guidelines did not recommend a restrictive or liberal transfusion strategy for hemodynamically stable patients with ACS. No specific mention of a suggested strategy for patients with CHF was made (21).

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More recently, an elegant observational study of approximately 35,000 AMI hospitalizations from 57 centers used propensity score analysis to identify a subset of patients who were well-matched on 45 variables. In this subset, transfusion was associated with a 25% reduction in the odds of hospital mortality (22). However, the accompanying editorial cautioned, that despite several observational studies on transfusion in patients with significant cardiac disease, there is still uncertainty on when to transfuse these patients (23). Nonetheless, there is arguably accumulating evidence that suggests that a restrictive transfusion strategy may not be optimal in this setting (13,14,19,22). Although another recent editorial echoed the sentiment that evidence on appropriate transfusion thresholds for patients with ACS is weak, the possibility was entertained that such patients may yet benefit from transfusion at higher Hgb levels (e.g., 9 to 10 g/dl) (24).

Due to this ongoing debate, we conducted additional analyses of a previously developed dataset to determine how Hgb level modifies the treatment effect of RBC transfusion during ICU admissions with respect to hospital mortality in the context of cardiac disease. Specifically, we sought to estimate the Hgb level below which transfusion is associated with reduced hospital mortality (or transfusion threshold) across key cardiac conditions, such as comorbid heart disease, AMI, unstable angina, and CHF. We hypothesized that transfusion thresholds with these conditions are higher than those advocated in the restrictive transfusion strategy. Ultimately, our goal was to assemble additional evidence to assist physicians in deciding when to transfuse critically ill patients with cardiac disease while we await the results of definitive clinical trials.

METHODS

We performed secondary analyses of Veterans Affairs (VA) electronic databases at the Center for Healthcare Organization and Implementation Research. Ethical approval was obtained from the VA Bedford Institutional Review Board. Individual-level data on VA ICU admissions during fiscal years 2001 through 2005 were extracted from national-level VA databases. For hospitals with separate surgical and neurological ICUs, we only selected medical ICU episodes. We excluded operative cases with surgical admitting diagnoses. Only the first ICU episode of each year for unique patients was included.

Hospital death was the outcome of interest, whereas RBC transfusion during the first 30 days of ICU admission was the treatment of interest. Transfusion receipt was defined as having an International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM) procedure code of 99.04 (transfusion of packed cells) or 99.03 (transfusion of whole blood) in the ICU file. ICU admissions with at least 1 transfusion documented during the first 30 days were collectively assigned as the "transfusion" group; all others were included in the "no transfusion" group. To exclude hospitals that were possible outliers in terms of transfusion practices, we arbitrarily removed data from 8 of 120 hospitals where transfusion rates were >2 SD from the mean.

To specify the nadir Hgb level, we selected the lowest value during ICU admission before blood transfusion. If not transfused, we selected the lowest value during the first 30 days of ICU admission. If none was available, we used the lowest value during hospital admission before ICU admission.

Other explanatory variables included demographic characteristics, admission-related information, comorbid conditions (e.g., Elixhauser comorbidity measures [25], Acute Physiology and Chronic Health Evaluation III chronic health parameters [26], and others [27,28]), ICU admission diagnoses categories (adapted from the Healthcare Cost and Utilization Project) (29), and selected blood test values. Comorbid conditions were assigned if their codes were stated at least once in administrative records during the previous 2 years, but not where there was an overlapping admission diagnosis (27). ICU admission diagnoses were defined by the first ICD-9-CM code from ICU files. Chronic kidney disease was defined as a glomerular filtration rate <60 ml/min/1.73 m^2 for at least 3 months (30).

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AMI = acute myocardial infarction

CHF = congestive heart failure

Hgb = hemoglobin

ICU = intensive care unit

RBC = red blood cell

RCT = randomized controlled trial

VA = Veterans Affairs