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Journal club critique

Randomized controlled trials are needed to determine appropriate blood transfusion strategies in patients with acute coronary syndromes

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Expanded Abstract

Citation

Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, Moliterno DJ, Lindblad L, Pieper K, Topol EJ, Stamler JS, Califf RM: Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 2004, 292:1555-1562 [1].

Background

It is unclear if blood transfusion in anemic patients with acute coronary syndromes is associated with improved survival.

Objective

To determine the association between blood transfusion and mortality among patients with acute coronary syndromes who develop bleeding, anemia, or both during their hospital course.

Methods

Design: Retrospective cohort analysis of prospectively collected clinical trial data.

Setting and Patients: 24,112 patients from three large international trials of patients with acute coronary syndromes (the GUSTO IIb, PURSUIT, and PARAGON B trials). Patients were grouped according to whether they received a blood transfusion during the hospitalization. The association between transfusion and outcome was assessed using Cox proportional hazards modeling that incorporated transfusion as a time-dependent covariate and the propensity to receive blood, and a landmark analysis.

Outcomes: The primary outcome was 30-day all-cause mortality, with a secondary composite endpoint of 30-day mortality or myocardial infarction (MI).

Results

Of the 24,112 patients, 2401 (10.0%) underwent at least one blood transfusion during their hospitalization. Those receiving blood were more likely to be older, female, black, have lower bodyweight, more comorbid illness, and ST segment depression on their initial EKG. Patients who underwent transfusion had a significantly higher unadjusted rate of 30-day death (8.00% vs. 3.08%; P<.001), MI (25.16% vs. 8.16%; P<.001), and death/MI (29.24% vs. 10.02%; P<.001) as compared with patients who did not undergo transfusion.

Using Cox proportional hazards modeling that incorporated transfusion as a time-dependent covariate and adjusted for baseline characteristics, bleeding, transfusion propensity, and nadir hematocrit, transfusion was associated with an increased hazard for 30-day death (adjusted hazard ratio [HR], 3.94; 95% confidence interval [CI], 3.26-4.75) and 30-day death/MI (HR, 2.92; 95% CI, 2.55-3.35). In the landmark analysis that included procedures and bleeding events, transfusion was associated with a trend toward increased mortality. The predicted probability of 30-day death was higher with transfusion at nadir hematocrit values above 25%. The adjusted odds ratios for 30-day death associated with transfusion by nadir hematocrit were: hematocrit 20% (OR, 1.59; 95% CI, 0.95-2.66), hematocrit 25% (OR, 1.13; 95% CI, 0.70-1.82), hematocrit 30% (OR, 168.64; 95% CI, 7.49-3797.69), and hematocrit 35% (OR, 291.64; 95% CI, 10.28-8273.85).

Conclusion

Blood transfusion in the setting of acute coronary syndromes is associated with higher mortality, and this relationship persists after adjustment for other predictive factors and timing of events. Given the limitations of post hoc analysis of clinical trials data, a randomized trial of transfusion strategies is warranted to resolve the disparity in results between our study and other observational studies. We suggest caution regarding the routine use of blood transfusion to maintain arbitrary hematocrit levels in stable patients with ischemic heart disease.

Commentary

Because the myocardium may be adversely affected by anemia in the presence of ischemic heart disease, clinicians have commonly used blood transfusions to maintain hematocrit values in patients with ischemic heart disease. The theory underlying this practice is that blood transfusion will increase oxygen delivery and improve outcomes in these patients. However, there is no definitive evidence to support this premise.

Recently, this practice, and transfusion practices in general, have come under increased scrutiny, as researchers have grappled with the question of appropriate transfusion thresholds and the potential harmful effects of transfusion, such as transfusion related lung injury, viral disease transmission, and immune suppression.

Fueling this controversy are a number of recent studies examining appropriate transfusion thresholds and target hematocrit values among critically ill patients (Table 1). Hébert and colleagues found that a restrictive strategy for red cell transfusion is at least as safe and possibly safer than a more liberal transfusion strategy when applied to a general population of ICU patients [2]. The restrictive strategy sought to maintain circulating hemoglobin concentrations ≥7.0 g/dL whereas the liberal strategy sought to maintain hemoglobin concentration ≥10.0 g/dL [2]. This study, however, raised concern that critically ill patients with cardiovascular disease might not fair well with the restrictive strategy. In a subsequent post hoc analysis of this trial, the same group found that the restrictive strategy generally appears to be safe in most critically ill patients with cardiovascular disease, with the possible exception of patients with acute myocardial infarction and unstable angina [3]. Others studies have supported this finding [4,5]. However, Wu and colleagues, in a large observational study utilizing 78,974 Medicare records, found that elderly patients with acute MI and an admission hematocrit less than 33% had lower 30-day mortality with blood transfusion than those who did not receive transfusion [6].

It is upon this background that we consider the present study by Rao and colleagues [1] which examined the association between blood transfusion and mortality in 24,122 patients with acute coronary syndromes enrolled in three large international trials (GUSTO IIb [7], PURSUIT [8], PARAGON [9]). They found that transfusion was associated with an increased hazard for death within a 30-day interval and that the odds of death were higher when transfusion occurred at hematocrit nadirs >25%. Based on these findings, the authors called for a randomized controlled trial of transfusion strategies in this patient population and recommended caution regarding the routine use of blood transfusion to maintain arbitrary hematocrit levels in patients with ischemic heart disease who are otherwise stable.

Table 1: Observational studies of transfusion strategies in patients with cardiovascular disease

Study	Patients	Transfusion Strategy	Conclusion
Hébert et al [2] TRICC	Critically ill patients	Restrictive: Hgb< 7 g/dL Liberal: Hgb<10 g/dL	No difference in mortality
Hébert et al [3] TRICC subgroup analysis	Critically ill patients with cardiovascular disease	Restrictive: Hgb<7 g/dL Liberal: Hgb<10 g/dL	No difference in mortality
Wu et al [6]	Elderly patients with acute MI	Hematocrit on admission	Transfusion associated with ↓ mortality when Hct<30%
Bush et al [4]	Patients undergoing elective vascular surgery	Restrictive: Hgb<9 g/dL Liberal: Hgb<10 g/dL	No difference in mortality or MI
Johnson et al [5]	Patients undergoing elective myocardial revascularization	Restrictive: Hct<25% Liberal: Hct<33%	No difference in MI, exercise tolerance, or cardiac index

Hgb = hemoglobin; Hct = hematocrit; MI = myocardial infarction

This study has a number of strengths, including a very large sample size, prospectively collected data, and the use a variety of robust statistical techniques to address potential biases, all of which reached the same conclusions. There are, however, a number of limitations that deserve consideration. First, this was a post hoc analysis of data from three clinical trials, none of which were designed to address the question of appropriate transfusion thresholds. Thus the study is hypothesis generating and not intended to prove cause and effect. Second, since transfusion was a post-randomization event, indication bias may have influenced the results. The authors do a good job of addressing this issue, including the use of a transfusion propensity score. However, the potential for this bias still exists. Third, because of the nature of the data, the authors were unable to include in their analyses consideration of the age of the blood transfused or if it was leukoreduced, characteristics that may influence the physiologic effect of transfusion. Finally, it is unclear whether these results can be applied to patients with cardiac disease who do not meet GUSTO IIb, PURSUIT, or PARAGON entry criteria, such as those with cardiovascular disease coincident to critical illness.

Recommendation

The results of this study justify the need for a multicenter clinical trial of different transfusion strategies in patients with acute coronary syndromes with mortality as the primary endpoint and with consideration of the age of the blood transfused and whether it was leukoreduced as important covariates. Until the results of such a trial, it remains clear that in otherwise stable intensive care unit patients without evidence of active bleeding or acute coronary syndromes, restrictive red-cell transfusion strategies appear to be safe and may lead to improved outcomes.

Competing interests

The authors declare that they have no competing interests.

References

1. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, Moliterno DJ, Lindblad L, Pieper K, Topol EJ, Stamler JS, Califf RM: **Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes**. *JAMA* 2004, **292**:1555-1562.
2. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: **A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group**. *N Engl J Med* 1999, **340**:409-417.
3. Hebert PC, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, Tweeddale M, Pagliarello G, Schweitzer I: **Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases?** *Crit Care Med* 2001, **29**:227-234.
4. Bush RL, Pevec WC, Holcroft JW: **A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients**. *Am J Surg* 1997, **174**:143-148.
5. Johnson RG, Thurer RL, Kruskall MS, Sirois C, Gervino EV, Critchlow J, Weintraub RM: **Comparison of two transfusion strategies after elective operations for myocardial revascularization**. *J Thorac Cardiovasc Surg* 1992, **104**:307-314.
6. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM: **Blood transfusion in elderly patients with acute myocardial infarction**. *N Engl J Med* 2001, **345**:1230-1236.
7. **A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb investigators**. *N Engl J Med* 1996, **335**:775-782.
8. **Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy**. *N Engl J Med* 1998, **339**:436-443.
9. Global Organization Network (PARAGON)-B Investigators: **Randomized, placebo-controlled trial of titrated intravenous lamifiban for acute coronary syndromes**. *Circulation* 2002, **105**:316-321.