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Blood transfusion in patients with acute MI and anaemia

Matthew W. Sherwood and Sunil V. Rao

The Duke Clinical Research Institute, North Pavilion 2400 Pratt Street Durham, NC 27705 USA

Abstract

In a meta-analysis of predominantly observational data, blood transfusion was independently associated with adverse outcomes in patients with myocardial infarction. These findings are consistent with previously published research, but clinical application of these data is hindered by the lack of prospective, randomized trials and the inherent bias in observational studies.

The appropriate use of blood transfusion for patients with acute myocardial infarction (MI) and anaemia remains controversial. Chatterjee and colleagues performed a meta-analysis of studies to determine the association between blood transfusion and outcomes among patients with MI, and found that transfusion was associated with an increase in all-cause mortality and recurrent infarction.¹ This study raises many questions, but two are particularly important. Why would transfusion be associated with harm among patients with acute MI? Is the study by Chatterjee sufficient to guide clinical practice?

To address these questions, we must review the pathophysiology of MI and the role that anaemia might have in outcomes. MI is a thrombotic event that is managed with a combination of antithrombotic therapy and invasive procedures, such as cardiac catheterization, percutaneous coronary intervention, or CABG surgery. This combination of treatment strategies places patients at risk of bleeding and subsequent anaemia. In addition, anaemia itself is known to exacerbate cardiac ischaemia,² thus creating a vicious cycle: treatment increases the risk of anaemia, which in turn can increase the risk of ischaemia. An obvious treatment option in the setting of either bleeding or anaemia is blood transfusion, because raising the haemoglobin content should, in theory, increase oxygen delivery to vulnerable myocardium. However, little high-quality data exist to guide either when or how much blood should be transfused in patients with MI. Studies indicate that up to 10% of patients with MI receive a transfusion during hospitalization,³ but risks are associated with transfusion of red blood cells, such as transmission of infectious agents, transfusion-associated circulatory overload, and transfusion-related lung injury.⁴ In addition, data suggest that packed red cells are rapidly depleted of nitric oxide during storage.⁴ This 'storage lesion' might reduce the ability of transfused blood to increase oxygen delivery and, therefore, might potentiate ischaemia, rather than reduce it, by inducing vasoconstriction and platelet activation.

Some published, prospective, randomized trials have examined 'transfusion thresholds' (that is, the level of haemoglobin at which transfusion should be given to maximize benefit and minimize harm), but most of these studies included a variety of critical illnesses, and very few patients with acute ischemic heart disease. Most of the literature focusing on transfusion strategies in this latter group includes either small, pilot, randomized trials or observational

Correspondence to: S. V. Rao sunil.rao@duke.edu.

Competing interests

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studies. The only published prospective, randomized trial is the CRIT Randomized Pilot trial,⁵ in which investigators randomly allocated 45 patients with MI, either with or without ST-segment elevation, and a haematocrit level $\geq 30\%$ within 72 h of admission, to either a liberal strategy (transfusion to maintain the haematocrit level at 30–33%) or a conservative strategy (transfusion to maintain the haematocrit level at 24–27%). The trial was not powered for any particular end point, but the rate of in-hospital death, recurrent MI, or congestive heart failure was compared between the groups. The rate of the composite end point was significantly higher among patients assigned to the liberal arm than in those allocated to the conservative arm (38% versus 13%; $P = 0.046$). This difference was driven by a higher incidence of heart failure with liberal transfusion. No significant differences occurred in the incidence of in-hospital mortality or recurrent MI.

This randomized trial was part of the meta-analysis performed by Chatterjee and co-workers, which also incorporated nine other observational studies that included *post-hoc* analyses of randomized trials examining antithrombotic therapies for MI, administrative data, and registries. The combination of these studies yielded a sample size of >203,000 patients. Two outcomes were assessed: all-cause mortality and MI reported after the longest-available duration of follow-up. The researchers went to great lengths to test for publication bias, using funnel plots, Egger regression tests, and trim-and-fill methods for odds ratio calculations, and found no evidence of bias. They also used meta-regression and sequential analyses to validate the findings statistically. After applying robust meta-analytic techniques, the investigators found that blood transfusion was independently associated with an increased risk of all-cause mortality (relative risk [RR] 2.91, 95% CI 2.46–3.44, $P < 0.001$), and recurrent MI (RR 2.04, 95% CI 1.06–3.93, $P = 0.03$).

Are these data sufficient to guide clinical practice? Should blood transfusion be withheld in patients with acute MI and anaemia? The short answer is ‘no’; the longer answer requires a review of the primary limitation of observational studies examining the role of transfusion. In an observational analysis, the association of transfusion with cardiovascular outcomes can suffer from confounding by indication—the idea that patients receiving an indicated therapy (for example, blood transfusion) might be more likely to experience an adverse outcome unrelated to the therapy. In the setting of an MI, patients with anaemia might have a higher risk of death and recurrent ischaemia, and are also more likely to receive a transfusion. The risk of adverse outcomes with anaemia might overwhelm any benefit of transfusion, thus creating an association between transfusion and the outcome that might not be causal. In most, if not all, of the observational studies included in the Chatterjee analysis, multivariable regression or propensity matching techniques were used to adjust for confounding variables, and although the researchers used meta-regression to overcome potential biases, unmeasured confounding is undoubtedly still present.

Given the lack of high-quality data from randomized trials, the American Association of Blood Banks has been hesitant to make strong recommendations for or against a particular transfusion strategy in patients with MI patients (Table 1).⁶ Moreover, the strength of their recommendation is listed as “uncertain”, which leaves clinicians in a quandary about how best to treat patients with MI and anaemia. What clinicians can—and should—do, however, is to minimize the risk of bleeding and subsequent transfusion during treatment for MI. This aim can be accomplished by assessing a patient’s risk of bleeding using available risk models,⁷ appropriately adjusting the dose of antithrombotic medications,⁸ using antithrombin agents associated with reduced bleeding risk,⁹ and using radial artery access for cardiac catheterization and percutaneous coronary intervention whenever possible.¹⁰ Ultimately, given the prevalence of MI, the risk associated with anaemia, the frequent use of transfusion in these patients, and the lack of high-quality data, a prospective, randomized trial of transfusion strategies is needed to guide clinical practice.

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Table 1

Current AABB guidelines for transfusion of red blood cells⁶

Patient population	AABB recommendation
General, hospitalized	Adherence to a restrictive transfusion strategy (7–8 g/dl) in stable patients
Hospitalized with pre-existing coronary artery disease	Adherence to a restrictive strategy in hospitalized patients with pre-existing cardiovascular disease, and consideration of transfusion for patients with symptoms or a haemoglobin level < 8 g/dl
Acute coronary syndrome	No recommendation for or against a liberal or restrictive transfusion threshold for hospitalized, haemodynamically stable patients with acute coronary syndrome

Abbreviation: AABB, American Association of Blood Banks.