The silent risks of blood transfusion

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Current Opinion in Anaesthesiology 2008, 21:664–668

Purpose of review

Clinical research has identified blood transfusion as an independent risk factor for immediate and long-term adverse outcomes, including an increased risk of death, myocardial infarction, stroke, renal failure, infection and malignancy. New findings have called into question the traditional assumptions clinicians utilize in evaluating the risks and benefits of blood transfusion. Appreciation of newly recognized risks is important for conserving scarce resources and optimizing patient outcomes.

Recent findings

Recent clinical outcomes research has examined the impact of blood transfusion on critically ill patients, trauma patients, patients undergoing cardiac surgery, patients experiencing acute coronary syndromes, oncology patients and others. These studies provide additional evidence of adverse outcomes associated with blood transfusion in a wide variety of clinical contexts.

Summary

The benefits of blood transfusion have never been conclusively demonstrated, but evidence of transfusion-related harm continues to accumulate. Given the transfusion triggers that currently predominate in clinical practice it appears that clinical outcomes could improve significantly with more widespread adoption of restrictive transfusion strategies.

Keywords

blood transfusion, cardiac surgery, clinical outcomes, interventional cardiology

Curr Opin Anaesthesiol 21:664–668

0952-7907

Introduction

Following dramatic decreases in the incidence of infectious disease transmission and ABO mismatch-related reactions, red blood cell (RBC) transfusion was generally considered to carry minimal risks while providing the unquestioned benefit of improving outcomes by increasing tissue oxygen delivery. Over the past two decades, these assumptions have been challenged by clinical research linking transfusion to previously unappreciated adverse outcomes. Blood transfusion has been linked to organ dysfunction, immunosuppression (increasing vulnerability to infection and malignancy) and decreased survival in a variety of clinical contexts. Recent studies have strengthened the link between transfusion and these unintended consequences, and basic research has also suggested potential mechanisms for these effects. Practice guidelines are beginning to reflect this new evidence.

Commonly emphasized risks of blood transfusion

Historically, the most significant risks of blood transfusion were felt to be infectious disease transmission and ABO mismatch hemolytic reactions. More recently, transfusion-related acute lung injury (TRALI) has been identified as a significant risk. Infectious complications of blood transfusion have decreased but not disappeared. Although risks vary by region, the risk of transmitting HIV or hepatitis C is roughly 1 in 2 million units transfused; hepatitis B is estimated to be transmitted between 1 and 200 times for every million units of blood transfused. In the USA, West Nile virus (WNV) contaminates 1 in 350 000 units transfused. The risk of death from sepsis related to blood contaminated by bacteria is roughly 1 per million units transfused. Although of less concern in North America and Europe, parasitic diseases including malaria and Chagas disease can pose a significant risk in endemic areas [1,2]. If our experience with HIV and WNV repeats itself, it is possible that newly discovered blood-borne pathogens could pose significant risks before effective screening methods are developed. Fatal ABO mismatch reactions occur with roughly the same frequency as viral transmission and TRALI may occur in 1 in 5000 transmissions.

Impact of blood transfusion on clinical outcomes: the Transfusion Requirements in Critical Care trial

Despite 100 years of experience with blood transfusion, studies attempting to understand its impact on clinical

outcomes are comparatively recent. The landmark Transfusion Requirements in Critical Care (TRICC) trial, published in 1999, is the only large (838 patients) prospective randomized trial that supports a causal link between blood transfusion and adverse outcomes in critically ill adults. When patients were randomized to liberal (transfusion threshold of hemoglobin <10 g/dl) or restrictive (transfusion threshold <7 g/dl) groups there was a significant increase in cardiac and pulmonary complications and a trend towards increased mortality in the liberal transfusion group. When younger (<55) or less critically ill [acute physiology and chronic health enquiry (APACHE) score <20] patients were considered, there was a statistically significant increase in mortality in patients who were more liberally transfused [3]. A recent randomized trial in critically ill children using a design similar to the TRICC trial found that patients randomized to liberal and restrictive transfusion strategies experienced similar outcomes [4•].

Transfusion in critical care and trauma patients

In addition to the TRICC trial, there have been many retrospective analyses in a variety of clinical contexts that link blood transfusion to adverse outcomes. The Anemia and Blood Transfusion in the Critically Ill – Current Clinical Practice in the United States (CRIT) study evaluated 4892 ICU patients and found that the number of blood transfusions was independently associated with length of stay and mortality [5]. A recent cohort analysis within the CRIT trial found an independent association of blood transfusion and the development of acute respiratory distress syndrome (ARDS) (adjusted odds ratios 2.74, $P < 0.0001$) [6•]. Yilmaz *et al.* [7] found that a lung protective ventilatory strategy coupled with a restrictive transfusion strategy reduced the incidence of acute lung injury from 28 to 10%. In the critically ill, recent studies have confirmed that blood transfusion is associated with an increased incidence of infection, decreased survival and increased length of stay in adults [8,9•] and in children [10,11].

Data prospectively collected on 15 534 trauma patients at Maryland Shock Trauma Center revealed that blood transfusion was independently associated with a threefold increase in mortality [12]. A recent study of 8215 blunt trauma patients adds support to a dose–response relationship between transfusion and mortality [13].

Transfusion and malignancy

Recent studies have strengthened the association between blood transfusion and vulnerability to malignancy. Transfusions given within 5–29 years prior to initial cancer diagnosis were found to be associated with a 26% increase in the risk of developing nonHodgkin's lymphoma [14]. Patients who received blood during hepatocellular carcinoma resection were found to have a 5-year cancer-related survival rate of 38% versus 67% in patients who avoided transfusion [15].

Transfusion in cardiac surgery

High blood product utilization, significant morbidity and mortality, and large existing clinical outcomes databases have made cardiac surgery patients a natural target of studies attempting to determine the impact of transfusion on outcomes. Studies in these patients have identified RBC transfusion as an independent variable associated with an increase in infectious complications, myocardial infarction (MI), stroke, renal failure, prolonged ventilation, atrial fibrillation, hospital length of stay and mortality [16,17,18•]. Although the immediate impact on survival is significantly greater, transfusion with as little as one unit of RBCs has been associated with decreased 10-year survival following coronary artery bypass grafting [19]. Recent studies have added to the weight of this evidence. Murphy *et al.* [20••], in reviewing outcomes in 8724 patients in the UK, found no benefit from transfusion for hematocrits as low as 21% (hemoglobin of 7 g/dl), and the risk of death within 30 days of surgery was almost six times greater for patients who received blood. In addition, transfused patients were more likely to experience increased infections and adverse outcomes characterized as ischemic complications (MI, renal compromise and stroke) [20••].

Recent studies attempting to explain adverse outcomes for women in cardiac surgery have shown that the decreased survival experienced by women can be explained by their propensity to receive blood transfusions; women have a smaller body surface area (and increased vulnerability to hemodilution when undergoing cardiopulmonary bypass) and a lower baseline hematocrit [21,22]. A recent report of 6000 coronary artery bypass patients demonstrated that inclusion of preoperative anemia and blood transfusion data into the Society of Thoracic Surgeons (STS) risk model eliminated female gender as a risk factor [23].

Transfusion for patients with acute coronary syndromes and myocardial infarction

The historic rationale for blood transfusion includes the purported benefit of improved oxygen delivery. The TRICC trial investigators raised concern about the applicability of restrictive transfusion triggers in patients with acute coronary syndromes. A subsequent subgroup analysis of patients with cardiovascular disease showed a trend towards increased survival in the liberal transfusion group, but transfusion also resulted in a statistically

significant increase in pulmonary edema and multiorgan system dysfunction [24]. Wu *et al.* [25] published an analysis based on Medicare administrative data that showed an improvement in survival for patients over 65 years treated for acute MI if they received blood transfusions when their admission hematocrit was less than 30. Subsequent studies based on prospectively collected data and more sophisticated statistical analysis suggested blood transfusion was a risk factor for death and MI in patients with acute coronary syndromes [26]. Rao *et al.* [27] found this association to be significant for patients who received blood for hematocrits more than 25%. Singla *et al.* [28] reported on 370 patients in the VA system who presented with anemia (hemoglobin <11.5 g/dl) and a suspected acute coronary syndrome. After risk adjustment, the risk of MI or death was increased by a factor of 2.5 in patients who received blood [28]. Jani *et al.* [29] reported on 4623 anemic patients undergoing a percutaneous coronary intervention 1 week following a MI. Men with a preprocedure hemoglobin less than 13 g/dl and women with a preprocedure hemoglobin less than 12 g/dl were classified as anemic. After propensity matching and multiple regression analysis, transfused patients were roughly two times more likely to die in hospital [29].

The impact of anemia on clinical outcomes

Anemia has been associated with increased morbidity and mortality in a wide variety of clinical contexts including MI [30], heart failure [31], and cardiac [32] as well as noncardiac surgery [33]. The CRIT study, in contrast, found that anemia predicted the risk that a patient would be transfused but did not predict any other significant outcomes. A study by the Northern New England Cardiovascular Disease Study Group initially stimulated an increase in blood transfusion throughout the region when it was reported that the lowest hematocrit on bypass was correlated with increased mortality and postoperative heart failure [34]. Subsequent analysis suggested that though anemia is a marker for poor outcomes, the tendency for anemic patients to be transfused explains much of the association; moreover, blood transfusions were associated with postoperative requirements for mechanical and inotropic support independent of the degree of anemia [35]. Aronson *et al.* [36•] found that nadir hemoglobin in hospitalized patients following MI predicted increased mortality. After risk adjustment, anemic patients who received blood were 50% more likely to die within the follow-up period (6–48 months) than anemic patients who avoided transfusion [36•]. Kulier *et al.* [37••] collected 7500 data points on 5065 patients undergoing coronary artery bypass grafting in an attempt to determine the impact of preoperative anemia on postoperative adverse events. Investigators found that low preoperative hemoglobin was a significant marker for severe underlying comorbidities [e.g. diabetes, renal failure, hypertension, current smoking, unstable angina and congestive heart failure (CHF)]. Adverse cardiac events were attributed to these concomitant risk factors, and adverse postoperative neurologic and renal outcomes were attributed directly to anemia. Multiple regression analysis showed that preoperative anemia and intraoperative blood transfusion were both independent risk factors for adverse outcomes. At the same hemoglobin level, the incidence of adverse outcomes increased significantly as a function of numbers of units of RBCs transfused [37••].

Efficacy of blood transfusion as therapy for anemia

Available evidence not only suggests that anemia predicts adverse outcomes but also suggests that correction of anemia by transfusion using current transfusion practices either provides no benefit or is harmful. Attempts to determine the significance of anemia therefore demands inclusion of transfusion as a risk factor. Murphy *et al.* [20••] found that ischemic complications (MI, neurologic and renal injury) were not decreased with blood transfusion irrespective of the patient's nadir hematocrit or comorbidities. The lack of benefit from blood transfusions in decreasing these complications might be explained because hemoglobin levels rarely limit oxygen delivery given the transfusion triggers that predominate in current clinical practice [38]. Possible mechanisms for the contribution of transfusion to ischemic complications include pro-inflammatory effects and storage defects. Stored RBCs are 2,3-diphosphoglycerate (DPG) deficient and consequently less adept at unloading oxygen. It has also been proposed that loss of nitric oxide activity in banked blood impairs the vasodilatory response to hypoxia [39], though the clinical significance of these findings is controversial [40]. Stored RBCs are also less deformable, possibly leading to sludging and capillary occlusion. If stored RBCs have greater affinity for oxygen and capillary flow is impaired, blood transfusion could increase mixed venous oxygen saturation while decreasing tissue oxygen delivery [41•].

Clinical data supporting a role for storage defects as a contributor to adverse outcomes appeared recently. Having previously contributed significantly to the evidence implicating blood transfusion as a risk factor for adverse outcomes following cardiac surgery, Koch *et al.* [42•] at the Cleveland Clinic retrospectively evaluated the impact of differences in RBC storage duration. Patients who received blood that was stored for more than 2 weeks prior to transfusion had a statistically significant increase in in-hospital mortality, prolonged intubation, renal failure and sepsis or septicemia [42•].

Current guidelines

In an effort to conserve a limited and expensive resource and minimize the injury caused by transfusion therapy, the STS and the Society of Cardiovascular Anesthesiologists have joined forces and recently produced a clinical practice guideline. Their guidelines emphasize that the benefits of transfusion have not been adequately demonstrated and that existing evidence is an imperfect guide to transfusion decisions. They suggest a transfusion trigger of hemoglobin less than 7 g/dl in postoperative cardiac surgery patients (class IIa recommendation). In addition, they suggest (class IIb recommendation) that it is 'not unreasonable to transfuse red cells in certain patients with critical noncardiac end-organ ischemia (e.g. central nervous system and gut) whose hemoglobin levels are as high as 10 g/dl, but more evidence to support this recommendation is required' [43••]. Given the growing evidence of an association between transfusion and ischemic outcomes, this last recommendation appears to be poorly supported by current data.

Citing Rao *et al.* [27] the Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology issued guidelines recommending transfusing all patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS) with hematocrits less than 25% [44]. Rao *et al.* [27] were able to show an association with adverse outcomes when patients were transfused for a hematocrit more than 25%, but there was no indication that transfusion for a hematocrit less than 25% was beneficial.

Conclusion

The historic assumptions that blood transfusion consistently provides effective therapy for anemia and poses minimal risks to patients has been called into question by two decades of accumulating clinical evidence. The primarily retrospective studies summarized here will always be vulnerable to the criticism that these associations between blood transfusion and adverse outcomes reflect the tendency of clinicians to transfuse patients who are sicker than estimated by current risk adjustment measures or that important confounders have been missed. In addition, mechanisms by which transfused blood appears to cause harm are still unclear. In the aggregate, however, these studies increase the probability that blood transfusion is an important contributor to morbidity and mortality. If the links between blood transfusion and previously underappreciated adverse outcomes are causal, the true risks of blood transfusion increase by orders of magnitude. The benefits of blood transfusion have never been conclusively demonstrated, but evidence of transfusion-related harm continues to accumulate. Given the transfusion triggers that currently predominate in clinical practice, it appears that clinical outcomes could improve significantly with more widespread adoption of restrictive transfusion strategies. Current transfusion guidelines are changing in an effort to incorporate new data emphasizing the previously silent risks of blood transfusion.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 691–692).

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