

Anemia Versus Transfusion: Does Blood Conservation Increase the Risk of Complications?

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Abstract

Orthopedic trauma patients are routinely transfused for anemia even when asymptomatic at rest, despite there being relatively little scientific evidence as to what level of anemia can be safely tolerated. Some surgeons prefer a more liberal approach, transfusing to keep hemoglobin (Hgb) levels at 7.0 g/dL or higher; others prefer a more conservative approach, allowing Hgb levels to drop below 7.0 g/dL.

We conducted a study to determine if a more conservative approach might put patients at higher risk of complications of severe anemia. We retrospectively reviewed the cases of 104 patients who were treated by a single surgeon at a level I academic trauma center and who were followed up for at least 1 year. Patients (ages 18-50 years) were divided into 2 groups by lowest Hgb level before first transfusion—under 7.0 g/dL and 7.0 g/dL or higher—and then by whether they had been transfused. Logistic regression analysis was performed. The primary outcome was postoperative complication.

There was no increased risk of complication related to anemia ($P = .3$). However, there was a significant risk of complication related to transfusion ($P < .01$). Furthermore, there was a dose-dependent effect with each unit transfused ($P = .02$). In young, healthy, asymptomatic orthopedic trauma patients, a more conservative transfusion strategy (vs a more liberal strategy) did not appear to carry higher risk.

More than 13 million units of blood are transfused each year. Although transfusion can certainly be lifesaving, numerous studies over the past 20 years have shown significant, dose-dependent increases in morbidity, mortality, and cost with each unit of packed red blood cells (pRBCs) transfused.¹ Transfusion is one of the most common interventions in the critically ill population; however the negative effects of transfusion-related infection are well

documented in the recent literature.¹⁻⁷ There is no question that transfusion of blood products can be lifesaving to acutely ill trauma patients, but there is little evidence regarding when transfusions are indicated in asymptomatic anemic patients who are no longer in need of acute resuscitation.

Several studies have analyzed healthy individuals with an isovolemic reduction in hemoglobin (Hgb) level to 5.0 g/dL.^{8,9} They have found no significant compromise in oxygen delivery to the tissues. Currently, there is a lack of clinical data to suggest adequate RBC transfusion endpoints in trauma surgery.¹⁰ Given the lack of evidence to support transfusion triggers for young, healthy, asymptomatic orthopedic trauma patients, we decided to investigate whether a more conservative transfusion strategy might be as safe as a more liberal strategy.

Materials and Methods

After obtaining approval from our institutional review board, we performed a retrospective observational cohort analysis of patients treated at a level I trauma center between September 2006 and February 2009. The trauma registry included all patients who underwent surgery performed by a single orthopedic fellowship-trained trauma surgeon. All patients who had a recorded Hgb level of 9.0 g/dL or less at any time during their admission were included; they were considered no longer volume-depleted after initial resuscitation. Exclusion criteria were age under 18 years or over 50 years; pregnancy; head injury; and preexisting heart, pulmonary, or renal disease.

Initially, 963 patients were identified as orthopedic trauma patients treated by Dr. Mullis within the defined period. After inclusion and exclusion criteria were used to limit this database, the charts of the 109 patients who met the above criteria were reviewed. By chart review or telephone follow-up, 104 patients with 1-year follow-up were identified, and their cases became the basis for our analysis. Demographic information, length of hospital stay, surgeries performed, number of pRBC units transfused, Hgb level prompting transfusion, lowest recorded Hgb level, complications, and Injury Severity Score (ISS) were recorded for each patient. Seventy-two patients (69%) were male, 32 (31%) female. Mean age of the study population was 33 years.

Patients were divided into 2 groups by lowest Hgb lev-

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el before first transfusion—under 7.0 g/dL and 7.0 g/dL or higher—and then by whether they had been transfused. General guidelines for erythrocyte transfusion on the orthopedic trauma service included patients who were symptomatic at rest (headache, dizziness, or shortness of breath) and asymptomatic patients with Hgb levels under 5.0 g/dL. For patients with varying (lesser) degrees of anemia, transfusion typically depended on clinical symptoms and overall decrease in Hgb level from that recorded on admission.

Patient charts were reviewed for complications extending through a 1-year period after initial discharge from the inpatient service. Patients who had not received follow-up treatment through a known outpatient clinic were contacted by telephone to ascertain outcome. Overall, 5 of the 109 patients were lost at 1-year follow-up, leaving 104 patients with 1-year follow-up (95%). Primary outcome of the study was postoperative complications. Superficial wound infection was defined as cellulitis near the surgical site within 1 year, requiring oral antibiotics; deep wound infection was defined as any related infection within 1 year of injury, requiring intravenous antibiotics or surgical débridement in the operating room. The review for complications included superficial infection, deep infection, urinary tract infection, pneumonia, pulmonary embolism, deep venous thrombosis, acute renal failure or insufficiency, nonunion, delayed union, compartment syndrome, osteomyelitis, nerve palsy, anoxic brain injury, cardiac ischemia or infarct, pancreatitis, and death.

Statistical Methods

The primary focus of this analysis was to determine if patients’ risk of complication at 1-year follow-up was affected by anemia—lowest recorded Hgb level before first transfusion for transfused patients, or lowest Hgb level during hospital stay for nontransfused patients—or whether transfusion itself might be a risk factor for complication. Multiple logistic regression models were used to determine the likelihood each

group would have a complication. The dependent variable was complication rate; the explanatory variables included whether the patient was transfused, anemia/Hgb level (under 7 g/dL vs 7 g/dL or higher), and the 2-way interaction. Other possible explanatory variables entered into the model were age, sex, ISS, and whether the patient had had multiple surgeries. As the sample size was small, these variables were entered into the regression model one at a time. Results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and P values. The analysis was performed with SAS Version 9.1 (SAS Institute, Cary, North Carolina). Tests were considered statistically significant with $P < .05$ and marginally significant with $P < .10$. OR above 1 indicated that the odds of a complication occurring were higher in the exposed group (transfused patients) than in the unexposed group (nontransfused patients).

Results

The charts of 104 patients were reviewed and included in this analysis. Sixty-two patients (60%) had received a transfusion; 42 (40%) had not. Before first transfusion, 21 (34%) of the 62 transfused patients had Hgb levels under 7.0 g/dL, and the other 41 (66%) had Hgb levels of 7.0 g/dL or higher. Of the 42 nontransfused patients, 8 (19%) had lowest Hgb levels under 7.0 g/dL, and the other 34 (81%) had Hgb levels of 7.0 g/dL or higher (Table 1).

The transfused patients, considering all levels of anemia, had a mean ISS of 16.1 (range, 1-45), a mean of 2.0 operations (range, 1-6), a mean hospital stay of 18 days (range, 1-73 days), and a mean age of 34 years (range, 18-50 years). The nontransfused patients, considering all levels of anemia, had a mean ISS of 14.1 (range, 4-43), a mean of 1.4 operations (range, 1-5), a mean hospital stay of 10 days (range, 1-42 days), and a mean age of 33 years (range, 18-50 years). In the transfusion group, the mean number of transfused pRBC units was 6.9 (range, 1-31), or 7.8 units for patients with Hgb levels under

Table 1. Demographic Statistics Show Number of Transfused and Nontransfused Patients Relative to Their Lowest Hemoglobin Level Either Before Transfusion or, If Not Transfused, During Their Hospital Stay

Variable	Transfused (n = 62)		Nontransfused (n = 42)		P ^a	
	Mean	SD	Mean	SD		
Injury Severity Score	16.1	10.5	14.1	9.2	.3337	
Operations, n	2.0	1.4	1.4	0.8	.0075 ^b	
Hospital stay, d	17.8	13.6	9.5	7.5	.0001 ^b	
	n	%	n	%		
Hemoglobin, g/dL	<7.0	21	33.9	8	19.0	.1211
	≥7.0	41	66.1	34	81.0	
Complications	Yes	41	66.1	17	40.5	.0153 ^b
	No	21	33.9	25	59.5	

^at test for continuous variables; Fisher exact test for categorical variables.
^bStatistically significant ($P < .05$)

7 g/dL and 6.4 units for patients with Hgb levels of 7 g/dL or higher. At 1-year follow-up, complications were observed in 41 (66%) of the 62 transfused patients and in 17 (40%) of the 42 nontransfused patients (Table 1). The different types of complications seen in each group are listed in Table 2.

Statistical Analysis

Patients were divided into 2 groups by Hgb level—under 7.0 g/dL and 7.0 g/dL or higher—and then by whether they received pRBC transfusion. In addition, which patients had a complication over a 1-year period were identified.

For each group, we calculated sample size, number of complications, complication rate, and 95% CI for proportions. For transfused patients with Hgb level of 7.0 g/dL or higher, the

complication rate was 71% (29/41). For nontransfused patients with Hgb of 7.0 g/dL or higher, the complication rate was 41% (14/34). Similarly, for transfused patients with Hgb under 7.0 g/dL, the complication rate was 57% (12/21). Last, for nontransfused patients with Hgb under 7.0 g/dL, the complication rate was 38% (3/8) (Table 3).

Transfused patients had a significantly higher risk of complication (OR, 3.1; 95% CI, 1.4-7.1; $P < .01$). Severity of anemia was not found to be independently associated with increased risk of complication (OR, 0.6; 95% CI, 0.3-1.6; $P = .33$) (Table 4). The interaction term was removed and eliminated from further analysis, as it was not found to be significant ($P = .45$).

Furthermore, the possibility of confounding variables (eg, age, sex, ISS, number of surgeries performed) was con-

Table 2. Specific Complications Within Transfused and Nontransfused Groups

Complication	Transfused		Nontransfused	
	Hgb, ≥ 7 g/dL (n = 41)	Hgb, < 7 g/dL (n = 21)	Hgb, ≥ 7 g/dL (n = 34)	Hgb, < 7 g/dL (n = 8)
None	12	10	20	5
Superficial infection (required oral antibiotics)	7	2	5	2
Deep infection (required IV antibiotics or repeat surgery)	12	6	4	—
Urinary tract infection	5	1	1	—
Pneumonia	5	—	—	—
Pulmonary embolism	—	—	1	—
Deep vein thrombosis	1	1	2	—
Acute renal failure/acute renal insufficiency	4	—	—	—
Nonunion	7	—	2	1
Delayed union	1	—	1	—
Compartment syndrome	1	—	1	—
Osteomyelitis	2	—	1	—
Nerve palsy	7	4	3	1
Anoxic brain injury	—	—	—	—
Cardiac complication	—	—	—	—
Pancreatitis	—	—	—	—
Death	1	1	—	—

Abbreviations: Hgb, hemoglobin; IV, intravenous.

Table 3. Complication Rate for Patients Relative to Their Lowest Hemoglobin Level Either Before Transfusion or, If Not Transfused, During Their Hospital Stay, and Whether Patients Received Transfusion

Transfusion	Hgb, g/dL	Total	No. of Patients With Complication	Complication Rate	95% CI
Yes	< 7	21	12	.571	0.340-0.782
	≥ 7	41	29	.707	0.545-0.839
No	< 7	8	3	.375	0.085-0.755
	≥ 7	34	14	.412	0.247-0.593

Abbreviations: CI, confidence interval; Hgb, hemoglobin.

Table 4. Risk of Complication Associated With Either Anemia or Transfusion

Variable	Odds Ratio	95% CI	P
Hemoglobin, <7 g/dL	0.635	0.255-1.577	.3273
Transfusion	3.104	1.350-7.140	.0077

Abbreviation: CI, confidence interval.

sidered by including them in the model one at a time. From these logistic regression models, which included whether patients were transfused and level of anemia, an increased risk of complication (OR, 1.8; 95% CI, 1.1-2.9; $P = .02$) was found for each additional surgery, while receiving transfusion remained statistically significant (OR, 2.5; 95% CI, 1.0-5.8; $P < .04$). Age, sex, and ISS were not shown to be significantly associated with an increased complication rate (P s = .71, .32, and .13, respectively).

We performed a subanalysis of the transfused patients to determine the impact of number of units transfused on complication rate. Each additional unit of pRBCs transfused increased the risk of complication, indicating a dose-dependent response (OR, 1.3; 95% CI, 1.04-1.51; $P = .02$).

Discussion

Transfusion is a generally accepted and common intervention both in the intensive care unit and in the perioperative period. However, there is little evidence to support routine transfusion of asymptomatic orthopedic trauma patients who are no longer within the initial resuscitative period after trauma. Nevertheless, the practice is routinely done based on expert opinion (level 5 evidence). The anemia protocol for our orthopedic trauma service routinely allowed the Hgb levels of asymptomatic healthy patients to drop to under 7.0 g/dL without transfusion; when other services were consulted or were primary, however, these asymptomatic patients were still routinely transfused based on practitioners' practice patterns and anecdotal experiences.

In hemodynamically unstable patients, there is no acceptable substitute for blood transfusion. Blood replacement remains essential in the case of acute hemorrhage. However, the complications associated with transfusion should lead us to avoid, or at least minimize, unnecessary transfusion in young asymptomatic patients who are not actively bleeding in the postresuscitative period. In our study, we did not seek causation of increased complications with transfusion but assessed whether the risk of anemia outweighed the risk of transfusion in young, healthy, asymptomatic trauma patients who were no longer in the initial resuscitation period.

Our study was designed to evaluate a conservative transfusion strategy used in orthopedic trauma patients. We hypothesized that the risk of anemia in these asymptomatic patients would be lower than the risk of transfusing asymptomatic patients in the perioperative period. In addition, we thought the level of anemia would play a less significant role in the postoperative complication rate relative to transfusion itself. Our results suggest that a more conservative transfusion strat-

egy of allowing asymptomatic patients to become and remain anemic even to a Hgb level of 5 g/dL may be as safe as a more liberal transfusion strategy of keeping patients at a Hgb level higher than 7 g/dL. In general, the complication rate was 66% for transfused patients and 40% for nontransfused patients. These results remain significant after correcting for possible confounding factors, including age, sex, ISS, and number of surgeries.

The results of this study do not suggest that there may not be complications associated with anemia; a 40% complication rate even in the nontransfused group is high. One might expect that patients who had isolated injuries and never developed anemia with an Hgb level under 9 g/dL might have an even lower complication rate. In the group used for inclusion in this study, however, there was not a significant increased risk for patients who tolerated a lower anemia (Hgb, <7 g/dL), whereas transfusion to keep the Hgb level above 7 g/dL appeared to correlate with a significant risk of complication and appeared to be dose-dependent. It should be noted that the complications in both the transfusion and anemia groups are not necessarily related to transfusion or anemia, as many factors in a retrospective study cannot be controlled. These findings simply suggest that it might be as safe to use a conservative transfusion strategy as a liberal transfusion strategy in this patient population.

Although our study is retrospective, prospective randomized studies in the elderly and in the critical care population have shown conservative transfusion guidelines are at least as safe as liberal transfusion strategies.^{2,11} One study randomized intensive care unit patients with Hgb levels under 9.0 g/dL to 2 groups, one with liberal and the other with restrictive protocols for pRBC unit transfusion.² The liberal group maintained Hgb levels between 10.0 and 12.0 g/dL, and the restricted group kept Hgb levels between 7.0 and 9.0 g/dL. Thirty-day mortality was significantly lower in less acutely ill patients and younger patients (<55 years old) in the restrictive group than in the liberal group. It was concluded that a restrictive strategy of RBC transfusion is at least as effective as, and possibly superior to, a liberal transfusion strategy in the critically ill when considering short- and long-term outcomes. Another prospective study randomized elderly patients ($N = 2016$) with hip fractures and cardiovascular risk factors to a liberal transfusion strategy (if Hgb level fell under 10 g/dL) or a restrictive transfusion strategy (if Hgb level fell under 8 g/dL). The study found no difference between the 2 groups.¹¹

The deleterious effect of allogeneic blood transfusion on the immune system is complex and has been linked to the down-regulation of cellular immunity, including decreased function of natural killer cells, decreased function of macrophages and monocytes, and increased numbers of suppressor T cells.^{12,13} This minimized immune response has been associated with a multitude of infectious morbidities in various patient populations.⁷ A meta-analysis of 20 studies reviewing outcomes of the effects of transfusion on postoperative bacterial infection found strong evidence supporting a correlation.⁵ Their analysis found an OR of 5.3 (range, 5.0-5.4) for infec-

tious complication after allogeneic transfusion in the trauma population, and an OR of 3.5 (range, 1.4-15.2) considering all patient populations.

Similar results showing increased risk of infectious morbidities associated with transfusion were found in other studies involving the critically ill, patients after hip arthroplasty, and cardiothoracic surgery and general trauma populations.^{1,3,4,14,15} Furthermore, these results were seen in a dose-dependent response leading to increased incidence of complication with each unit of blood transfused.

Our study did not focus only on infection but included other complications (eg, cardiac, renal, and brain ischemia) that might be associated with anemia or transfusion. It is intuitive that anemia can cause ischemic events but less intuitive that allogeneic transfusion can also cause ischemic events because of the poor deformability of the cells due to storage, which can lead to “sludging” in capillaries throughout the body.¹⁶ This has been shown to be important in animal models, but it is unclear what poses more risk in humans—anemia without transfusion or the initial insult from transfusion, before the body clears the “waste” from stored cells and the remaining viable cells gain oxygen-carrying capacity.

Our study has several limitations. The number of patients who had severe anemia (Hgb level, <7 g/dL) and were not transfused is relatively small compared with the numbers in the other groups used for comparison. Because our study was retrospective, we could only find associations and not prove causation. This is significant, as the higher complication rate seen with transfusions may only be caused by the transfusion as a predictor of a patient requiring more complex surgery with higher blood loss (and higher risk of complication) or other such risk factors that led to transfusion, but not the transfusion itself causing the complication. An attempt was made to remove this potential bias by controlling for age, sex, ISS, and whether the patient had multiple surgeries. However, there may have been other significant confounding variables not excluded. As complications were assessed by chart review, they may not include those that occurred at other institutions and that were never reported to the practitioners at our facility (though we did have the ability to search records of neighboring institutions electronically when electronic medical records were available). That no functional outcomes were included in this retrospective review might make the complication rate appear more or less sensitive than the patients’ own opinions regarding their outcomes. All these weaknesses could call into question whether the statistically significant higher risk associated with allogeneic transfusion found in this study is real, but the focus and reason for pursuing this study were to determine if permissive anemia was dangerous or would be associated with a higher risk of complications than routine allogeneic transfusion of asymptomatic patients to treat a laboratory value.

Strengths of the study include the review of a single surgeon’s practice with a written protocol in place for anemic orthopedic trauma patients. The 95% follow-up (104/109 patients) is good for this type of trauma population. Although this

series is retrospective, it is reasonably large for a subgroup of young, healthy orthopedic trauma patients to study the effects of anemia or transfusion. Whether transfused or not, many of these patients tolerated Hgb levels under 7 g/dL, which gave a large enough comparison group to evaluate the independent effects of transfusion (or of using transfusion as a marker for complication risk) or anemia as a risk factor. As a result, it appears that a more conservative transfusion strategy may be as safe as a more liberal transfusion strategy. The results of this retrospective study were used to design a prospective multidisciplinary pilot study randomizing patients to either a liberal or a conservative transfusion strategy to determine which approach might carry higher risks of complications.

Conclusion

The results of this retrospective study suggest that a conservative transfusion strategy in a young, healthy, euvoletic asymptomatic patient who is not actively bleeding may be as safe as a liberal transfusion strategy and potentially may have fewer complications than does transfusion for a conventional laboratory value. Our study results do not suggest that transfusions should be held in patients who are symptomatic at rest or in patients who are being actively resuscitated, as transfusion can be lifesaving under these circumstances. A prospective randomized study has begun at our institution with enrollment expected to take 2 years with another year needed to complete 1-year follow-up of all patients.

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