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CRITICAL CARE

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Blood transfusion for upper gastrointestinal bleeding: is less more again?

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Abstract

Background: The hemoglobin threshold for transfusion of red blood cells in patients with acute gastrointestinal (GI) bleeding is controversial. We compared the efficacy and safety of a restrictive transfusion strategy with those of a liberal transfusion strategy.

Methods: *Objective:* The objective was to prove that the restrictive threshold for red blood cell transfusion in patients with acute upper GI bleeding (UGIB) was safer and more effective than a liberal transfusion strategy.
Design: A single-center, randomized controlled trial was conducted.
Setting: Patients with GI bleeding were admitted to the de la Santa Creu i Sant Pau hospital in Barcelona, Spain.
Subjects: The subjects were adult intensive care unit patients admitted with high clinical suspicion of UGIB (hematomemesis, melena, or both). Patients were excluded if they had massive exsanguinating bleeding, acute coronary syndrome, symptomatic peripheral vascular disease, stroke/transient ischemic attack, transfusion within the previous 90 days, recent trauma or surgery, lower GI bleeding, or a clinical Rockall score of 0 with hemoglobin higher than 12 g/dL.
Intervention: A total of 921 patients with severe acute UGIB were enrolled. Of these, 461 were randomly assigned to a restrictive strategy (transfusion when the hemoglobin level fell to below 7 g/dL) and 460 to a liberal strategy (transfusion when the hemoglobin fell to below 9 g/dL). Random assignment was stratified according to the presence or absence of liver cirrhosis.
Outcomes: The primary outcome was rate of death from any cause within the first 45 days. Secondary outcomes were further bleeding, defined as hematemesis or melena with hemodynamic instability or hemoglobin decrease of 2 g/dL or more, and in-hospital complications.

Results: In total, 225 patients assigned to the restrictive strategy (51%) and 65 assigned to the liberal strategy (15%) did not receive transfusions (P <0.001). The probability of survival at 6 weeks was higher in the restrictive-strategy group than in the liberal-strategy group (95% versus 91%; hazard ratio (HR) for death with restrictive strategy, 0.55; 95% confidence interval (CI) 0.33 to 0.92; P = 0.02). Further bleeding occurred in 10% of the patients in the restrictive-strategy group and in 16% of the patients in the liberal-strategy group (P = 0.01), and adverse events occurred in 40% and 48%, respectively (P = 0.02). The probability of survival was slightly higher with the restrictive strategy than with the liberal strategy in the subgroup of patients who had bleeding associated with a peptic ulcer (HR 0.70, 95% CI 0.26 to 1.25) and was significantly higher in the subgroup of patients with cirrhosis and Child-Pugh class A or B disease (HR 0.30, 95% CI 0.11 to 0.85) but not in those with cirrhosis and Child-Pugh class C disease (HR 1.04, 95% CI 0.45 to 2.37). Within the first 5 days, the portal-pressure gradient increased significantly in patients assigned to the liberal strategy (P = 0.03) but not in those assigned to the restrictive strategy.

Conclusions: Compared with a liberal transfusion strategy, a restrictive strategy significantly improved outcomes in patients with acute UGIB.

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Commentary

The annual incidence of hospitalization for acute UGIB is 1 in 1,000 people in North America, translating to 300,000 admissions yearly [1] and a total annual expenditure of $2.5 billion [2]. The mortality from UGIB is approximately 10% and may reach 35% in patients hospitalized with another medical condition [3].

In the critically ill, a more restrictive strategy has been used for blood transfusion on the basis of a growing body of data indicating worse outcomes with red blood cell transfusions in this population [4,5]. However, the threshold for blood transfusion in patients with UGIB has been controversial since hemoglobin values may underestimate the blood loss. Over the past decade, consensus guidelines suggested using a more conservative approach based on experimental studies, trials in other populations, and physiologic data [6,7]. A prospective observational study in patients with UGIB showed that blood transfusion in the first 12 hours in patients presenting with hemoglobin of more than 8 g/dL increased mortality and rebleeding rates in comparison with patients not receiving blood transfusion in the first 12 hours [8]. A recent Cochrane meta-analysis of randomized controlled trials examining red blood cell transfusion for the management of UGIB found only three trials and showed higher mortality and rebleeding rates for a liberal transfusion strategy. However, these studies had design flaws and were underpowered [9].

The Transfusion Strategies for Acute Upper Gastrointestinal Bleeding trial [10] is a randomized controlled trial testing liberal and conservative strategies for patients with UGIB. The authors hypothesized that a restrictive threshold for red blood cell transfusion (transfusion when hemoglobin was below 7 g/dL with a goal of 7 to 9 g/dL) was safer and more effective than a liberal transfusion strategy (transfusion when hemoglobin was below 9 g/dL with a goal of 9 to 11 g/dL). Patients with low mortality and low risk of rebleeding were excluded by using the Rockall score, which is based on age, presence or absence of shock, comorbidities, reason for bleeding, and major stigmata of recent hemorrhage [11]. The primary endpoint was all-cause mortality rate at 45 days. Secondary outcomes were rebleeding rate and adverse events. The random assignment was stratified by the presence or absence of cirrhosis. Twenty-eight percent in the restrictive group and 31% in the liberal group were in shock upon enrollment. The restrictive-strategy group had a lower mortality rate than the liberal group (5% versus 9%, $P = 0.02$) at 45 days, and the relative-risk reduction was 45% and the number needed to treat was 25 patients for the restrictive strategy intervention. In addition, the liberal-strategy group had higher frequency of rebleeding, interventions (transjugular intrahepatic portosystemic shunt for variceal bleeding and surgery in non-variceal bleeding), and cardiac and pulmonary adverse effects.

The study had several strengths. First, it used a randomized controlled design and a patient-centered outcome with an adequate number of patients. The protocol was well devised for hemoglobin checks and management of complications. The study also had a few concerns. The protocol allowed the physicians to transfuse in the presence of signs and symptoms of anemia in case of a massive bleed and if a surgical intervention was planned. However, protocol violations in transfusing blood occurred in both arms, and more violations occurred in the restrictive group (9% versus 3%).

Multiple mechanisms have been suggested by previous animal and physiologic studies to explain the increased mortality and morbidity with a liberal transfusion strategy [12-14]. These include clot rupture, coagulopathy, changes in stored red blood cells (the storage lesion), and immunomodulation. The duration of storage of red blood cells was similar in the two groups, and the coagulation laboratory test results were also similar in the two groups [15], suggesting that these pathways may not solely explain differences in outcomes.

Although this study was conducted only in patients with UGIB, a similar restrictive approach should be considered by physicians caring for critically ill patients presenting with other acute bleeding episodes, such as lower GI bleeding and retroperitoneal bleeding. However, physicians should be careful about extrapolating these results to patients with massive bleeding or those with bleeding and acute coronary syndrome.

Recommendation

A restrictive strategy for blood transfusions should be used for UGIB. The results of this study reinforce the growing notion that 'less is more' for a blood transfusion strategy in the critically ill.

Abbreviations

CI: Confidence interval; GI: Gastrointestinal bleeding; HR: Hazard ratio; UGIB: Upper gastrointestinal bleeding.

Competing interests

The authors declare that they have no competing interests.

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