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To Transfuse or not to Transfuse in Upper Gastrointestinal Hemorrhage? That is the Question

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Abstract

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

Methods—We enrolled 921 patients with severe acute upper gastrointestinal bleeding and randomly assigned 461 of them to a restrictive strategy (transfusion when the hemoglobin level fell below 7 g per deciliter) and 460 to a liberal strategy (transfusion when the hemoglobin fell below 9 g per deciliter). Randomization was stratified according to the presence or absence of liver cirrhosis.

Results—A total of 225 patients assigned to the restrictive strategy (51%), as compared with 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% vs. 91%; hazard ratio 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 as compared with 16% of the patients in the liberal-strategy group (P = 0.01), and adverse events occurred in 40% as compared with 48% (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 (hazard ratio, 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 (hazard ratio, 0.30; 95% CI, 0.11 to 0.85), but not in those with cirrhosis and Child–Pugh class C disease (hazard ratio, 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—As compared with a liberal transfusion strategy, a restrictive strategy significantly improved outcomes in patients with acute upper gastrointestinal bleeding.

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Upper gastrointestinal bleeding is caused by many different lesions and varies greatly in severity, ranging from clinically insignificant to life threatening. It is common, accounting for around 300,000 admissions per year in the United States (1, 2). The most common causes of upper gastrointestinal bleeding in the United States include peptic ulcer disease and esophagogastric varices (3). Outcomes in upper gastrointestinal bleeding, specifically caused by esophageal varices have improved, at least over the last 20 years – in parallel with the routine introduction of esophageal band ligation, use of pharmacologic agents, and prophylaxis against bacterial infections with antibiotics (4).

Multiple variables in acute upper gastrointestinal bleeding appear to help predict outcome - including the presence of certain symptoms (bright red bleeding), signs (hypotension on presentation), and laboratory features (elevated Model for End Stage Liver Disease (MELD) score in cirrhotics). One of the more controversial variables in assessment of prognosis in gastrointestinal bleeding is that of the “red blood cell” volume or mass (i.e., hematocrit or hemoglobin). In some studies, initial hemoglobin or hematocrit levels have been shown to be associated with outcome (5), while in other studies the level of hematocrit or hemoglobin was not important in predicting outcome (3, 6). Specifically in patients with cirrhosis, a recent study of a large number of patients with upper gastrointestinal bleeding suggested that the combination of MELD score, need for use of pressors, and albumin, and not the hematocrit level, were the most meaningful predictors of outcome, regardless of the cause of bleeding (7). While volume resuscitation is clearly important in patients with volume depletion, by inference, these data have raised questions about the importance of aggressive transfusion in patients with acute upper gastrointestinal bleeding. Further, in patients with portal hypertension, transfusion of blood products may increase portal pressure or alter coagulation parameters and lead to rebleeding (8, 9).

Once a patient with upper gastrointestinal bleeding presents to the hospital, current practice is to address that particular patient’s hemodynamic stability and administer intravenous colloids and transfuse blood (PRBCs) to correct hemodynamics and the hematocrit level. Unfortunately, little data exist about how to best transfuse blood, and practice in the United States has evolved into a scenario in which blood is often arbitrarily transfused to a “hematocrit of 30” or “hemoglobin of 10”, depending on ones preference for hematocrit or hemoglobin. For that matter, fresh frozen plasma is also often given to correct the INR (typically to <1.6 and platelets are given to raise counts >50K). However, meaningful endpoints are unfortunately often lacking. This becomes a problematic approach because it is clear that blood transfusion has risks, and a variety of studies in the setting of trauma, in the intensive care unit, and in other situations have demonstrated that blood transfusion may have deleterious effects (10–12).

The study by Villaneuva et al (13) demonstrated that a “restrictive” hemoglobin threshold for transfusion of 7 g/dL hemoglobin per deciliter compared to a “liberal” a threshold of 9 g/dL per deciliter, was associated with a 45% relative-risk reduction in 45-day mortality.

Mortality was significantly improved in patients with esophageal variceal hemorrhage, but not in patients with peptic ulcer bleeding. Some details of the study are noteworthy. First, in all patients with cirrhosis, rebleeding was lower in patients in the restrictive group than in the liberal transfusion group (16/139 [12%] vs. 31/138 [22%], p = 0.02), although this difference appeared to be limited to those with Child-Pugh A/B scores, and was not evident in patients with Child-Pugh C cirrhosis. Further, the decrease in mortality was accounted for primarily by fewer deaths from bleeding that could not be successfully controlled.

Among the most compelling data from the study were those that demonstrated transfusion was associated with increases in hepatic venous pressure gradient (HVPG). Remarkably, an HVPG was obtained in 86 patients in the restrictive transfusion group and in 89 in the liberal transfusion group within the first 48 hours after presentation, and was repeated 2 to 3 days later in 74 and 77 patients, respectively. Patients in the liberal transfusion arm had a significant increase in the mean HVPG between the first and second measurements (from 20.5 ± 3.1 mm Hg to 21.4 ± 4.3 mm Hg, p = 0.03). There was no significant change in the mean HVPG in the restrictive transfusion arm. There are two important points concerning these data; the first is that it was not clearly reported as to how much blood was given between the HVPG measurement, and the second is that this is a very small increase in HVPG, and may not be clinically meaningful. Common sense suggests that the more blood given, particularly in the setting in which bleeding has stopped, the greater the change in HVPG.

A further important detail in the study is that all the patients underwent emergency gastroscopy within the first 6 hours of presentation. The routine use of such “urgent” endoscopy would be generally considered to be highly aggressive, and the practice of performing emergency endoscopy has become highly controversial. For example, many practioners intentionally defer endoscopy until after the patient has been fully volume resuscitated and become hemodynamically stable. This practice has been justified on the basis that performing so called “early endoscopy” has failed to demonstrate improvement in mortality (14–17). However, it has been demonstrated that performing endoscopy even in patients with low hematocrits is safe (3).

From a practical standpoint, urgent endoscopy and therapy would be expected to stop ongoing bleeding (at least in the majority of patients), and several studies suggest that early endoscopy improves outcomes (18, 19) or quality of care (17). This in turn would be expected to reduce transfusion demand. Thus, an important question has to do with the effect of early endoscopy in the context of a restrictive blood transfusion approach. One could argue that in the current study, while it would have been expected for there to be a reduction in the need for blood transfusion in both arms (since all patients underwent early endoscopy), it very well may be that aggressive early endoscopy played a role in definitively treating lesions so that blood transfusion was in fact not necessary - contributing to an improved outcome.

A key question at this point is how to integrate the findings from this study into the management of patients with upper gastrointestinal bleeding, and in particular those with cirrhosis and portal hypertension. Whether the practice reported in this single center study is

generalizable to a wider clinical audience remains unknown, particularly given the issues surrounding aggressive early endoscopy. Even though stopping bleeding early with mechanical endoscopic therapy makes good common sense, the results are not likely to be generalizable to most practices in the United States, primarily because truly early endoscopy and aggressive intervention is not often performed. Nonetheless, any decision to transfuse blood or blood products must take into account the risks and benefits associated with transfusion. Although the data from the Villaneuva study suggest that less aggressive blood transfusion is beneficial, experienced clinicians would all likely agree that the decision to transfuse is complex and should not be predicated solely on a specific hemoglobin/hematocrit value. Indeed, further studies on the issues surrounding blood transfusion as well as the role of early endoscopy in patients with upper gastrointestinal bleeding are clearly needed.

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