When to decide for transfusion in patients with liver cirrhosis and acute bleeding from esophageal varices? Liberal *versus* restrictive approach

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Introduction

Acute upper gastrointestinal (GI) bleeding is a common medical emergency that can result in life threatening haemorrhage and, therefore, it is associated with high risk of morbidity, mortality and high health care costs (1). Incidence of acute upper GI bleeding in the UK ranges between 100–150 per 100,000 adults annually, resulting in 70,000 hospital admissions every year (1). Upper GI hemorrhage represents one of the leading medical indication for blood transfusion, and accounts for 14% of all red blood cell (RBC) transfusions in England (2).

Variceal bleeding, defined as bleeding from an esophageal or gastric varix at the time of endoscopy or the presence of large esophageal varices with blood in the stomach and no other recognisable cause of bleeding (3), accounts for 10–15% of acute upper GI bleeding events and occurs mostly in patients with liver cirrhosis. Cirrhosis, the end stage of any chronic liver disease, is characterized by an increase in portal blood pressure due to increased blood flow resistance through the liver (4). Portal hypertension is responsible for the dilatation of the portosystemic venous connections and gastroesophageal variceal formation (5).

Due to the important role of liver in normal hemostasis, cirrhosis is considered as a complex-acquired coagulopathy. Although cirrhosis is often deemed as a condition with an increased risk of bleeding, patients with stable cirrhosis are in a state of rebalanced hemostasis (6). Minimal shift out of balance is capable of moving the patient to either hypocoagulable or a hypercoagulable state (6). Connection between variceal bleeding and cirrhosis-associated coagulopathy is without any strong evidence. Standard fresh frozen plasma doses (10–15 mL/kg) are unsatisfactory to elevate individual coagulation factor levels, unrelated to cirrhosis (1). Efforts aimed to correct abnormal laboratory values with therapeutic transfusion may worsen the bleeding due to volume overload and an increase in intravascular pressure (6).

RBC transfusion and acute upper GI hemorrhage

The massive loss of blood volume in acute GI bleeding can cause disturbances in regional and global oxygen delivery and therefore endanger tissue perfusion of vital organs (2,7). Although the benefit of blood transfusion is unquestionable in patients with massive blood loss, most cases of upper GI bleeding do not represent major bleeding and don't have the elements of hemodynamic instability (7). Blood transfusion

is not just a RBC replacement, but has a number of other effects, including potential immunological, infective and metabolic complications (8).

Exact mechanism which might be associated with further bleeding in cirrhotic patients with acute upper GI bleeding is not fully elucidated. As previously mentioned, in cirrhosis, increased portal pressure is responsible for the gastroesophageal variceal formation and pressure within the varix is one of the predictors of variceal rupture and subsequent hemorrhage (5). In an animal model of portal hypertension, transfusion of blood volume after induced hemorrhage elevated portal pressures above prehemorrhage levels. This was associated with an increase of portocollateral resistance due to vasoactive mediator release during hypovolemia (4). Therefore, transfusion may impair the splanchnic vasoconstrictive response caused by hypovolemia, hence inducing an increase in blood flow and pressure of the splanchnic system (9). Similar effect of blood transfusion on the increase of portal pressure has been shown in clinical trials during acute variceal bleeding (10).

In case of massive blood loss during variceal hemorrhage, hemoglobin level does not necessarily represent an accurate quantification of hemorrhage and may underestimate the severity of blood loss (4). Therefore, the hemoglobin threshold for blood transfusion in patients with acute upper GI bleeding has been controversial (11). Clinical practice regarding blood transfusion was previously cornered round "10/30 rule", thus referring to hemoglobin level in g/dL and hematocrit %, respectively (12,13). Old guidelines were also recommending RBC transfusion when the hemoglobin was 100 g/L or less (14).

Recent guidelines, such as U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients (3) and Baverno VI Consensus (15) recommended that a restrictive transfusion policy aiming for a haemoglobin of 70–80 g/L is suggested in haemodynamically stable patients, although transfusion policy in individual patients should also consider other factors such as cardiovascular disorders, age, hemodynamic status and ongoing bleeding (3,15). However, it has been shown in a nationwide study in the UK that 26% of patients with upper GI bleeding received RBC transfusion when the hemoglobin level was above 80 g/L and that the majority of patients with acute upper GI bleeding (56%) had a hemoglobin level above 70 g/L when they received RBC transfusion (16). It has also been shown that roughly one quarter of gastroenterologists in Canada are not following current guidelines and are overtransfusing hemodynamically stable patients with upper GI bleeding (17). Overtransfusion, a situation defined as an RBC transfusion in excess of requirements, has strong potential for detrimental effects (8). There are several reasons why overtransfusion is relatively frequent. First, a hemoglobin threshold of 100 g/L has been a standard medical practice for decades and time is needed to change the mindset of physicians. Second, quantifying blood loss in case of massive hemorrhage can be challenging, even more due to fact that the hemoglobin level does not have to represent an accurate quantification of blood loss (8).

Trials regarding acute upper GI bleeding and RBC transfusions

Since there are significant variations and inconsistencies associated with RBC transfusion protocols in a situation of acute upper GI bleeding, a number of studies have been conducted to elucidate current uncertainties regarding transfusion practices in upper GI hemorrhage.

There is growing body of evidence that early RBC transfusion is associated with an increase in rate of further bleeding and mortality (2,18-20). Patients that have acute upper GI bleeding and received an RBC transfusion within 12 hours of admission have a twofold increase in rate of further bleeding and statistically non-significant tendency towards increased mortality (18). Similar to that, it has been shown that transfusion of RBC for patients with non-variceal upper GI bleeding within 24 hours of admission to hospital was significantly associated with an increased possibility of rebleeding, but not death (2). Further, in a study of acute non-variceal upper GI bleeding, early RBC transfusion was associated with an increased probability of further bleeding. The risk was limited to patients that were presented with a hemoglobin level of more than 90 g/L (19). Furthermore, retrospective cohort study conducted by the Chen *et al.* (20) found that RBC transfusion was significantly correlated with an increased rate of mortality and rebleeding in patients with acute upper GI bleeding (20).

Villanueva *et al.* (9) conducted a large, single-center, randomized controlled trial in which they compared restrictive (transfusion when hemoglobin level was below 70 g/L) versus liberal transfusion approach (transfusion when hemoglobin level was below 90 g/L) in patients with acute upper GI bleeding. This study shows that restrictive transfusion approach, when compared with the liberal

transfusion approach, significantly increased chance of survival at 6 weeks (95% *vs.* 91%), reduced risk of further bleeding (10% *vs.* 16%) and reduced risk of adverse events (40% *vs.* 48%). Furthermore, in the first 5 days, the portal-pressure gradient significantly increased in patients in the liberal strategy, but not in those in the restrictive strategy group. However, it needs to be outlined that this trial excluded patients with major comorbidities, such as ischemic heart disease, peripheral vascular disease or cerebrovascular disease, and therefore, may not represent a substantial number of patients with the greatest potential of complications from acute anemia. In addition, the treatment effect was only significant for cirrhotic patients with variceal hemorrhage, with no difference observed in mortality and rebleeding rates in patients with peptic ulcer bleeding, wherein this group of patients forms the largest group of patients with acute upper GI bleeding (9,21).

Jairath *et al.* (21) conducted a multi-centre, cluster randomized trial of transfusion strategies for acute upper GI bleeding. Hospitals were randomised to perform liberal or restrictive transfusion strategy so that all patients eligible for the study were managed according to the randomised strategy. Overall, there was no significant reduction in RBC transfusion and no significant difference in clinical outcomes (21). However, this study shows that the restrictive strategy of blood transfusion is at least safe and feasible in acute upper GI bleeding (21).

Odutayo *et al.* (22) conducted a systematic review and meta-analysis of randomised control trial comparing restrictive versus liberal blood transfusions. Five trials were included with a note that the trials from Villanueva *et al.* (9) and Jairath *et al.* (21) contributed to 93% of the total study participants. This study showed that in the restrictive strategy group the number of transfused RBC units was lower, as well as was the risk of rebleeding and overall mortality, without increased risk of the ischemic events (22).

A case report from the General Hospital of Shenyang Military Area

A group of authors from the General Hospital of Shenyang Military Area has shown a case of patient suffering from liver cirrhosis with acute bleeding from upper GI tract that has repeatedly developed hematemesis after transfusion (23). It was a patient who was hospitalized because of intermittent hematemesis and melena for about 12 days prior to the admission. He suffered from hepatitis B back 20 years, and liver cirrhosis has been established 10 years ago. At the local hospital prior to this hospitalization, an urgent endoscopy was performed, which determined the esophageal varices with a maximum diameter of 6 mm and a characteristic "red cherry" sign, but no endoscopic treatment was performed. Computerized tomography described liver cirrhosis with ascites, gastroesophageal varices, splenomegaly, portal vein thrombosis, fistula between the hepatic artery and portal vein and the edema of the ascending colon wall. Immediately upon arrival at Shenyang Hospital, he developed a hematemesis and lost about 600 mL of fresh blood. After hematemesis, blood pressure was 110/87 mmHg, heart rate was 87/min, and peripheral blood saturation 100%. There are therefore no clinical signs of hemodynamic shock. In the laboratory findings shortly after hematemesis there were no signs of anemia (the value of the absolute number of erythrocytes was 3.27×10^{12}/L, hemoglobin was 128 g/L and hematocrit 30.3%), as well as coagulopathy (prothrombin time 14.4 s, INR was 1.14).

The blood count immediately after the bleeding episode do not necessarily have to be altered because both erythrocytes and plasma are lost by bleeding, so according to the first finding we cannot conclude indirectly about the volume of blood that the patient lost with bleeding. Therefore, the condition of the patient and the hemodynamic parameters should be carefully monitored and the blood image repeated, as the transition from extracellular fluid to intravascular space will result in hemodilution and manifest post-hemorrhagic anemia.

A patient treated at the General Hospital of Shenyang Military Area was immediately ordered 3 doses of erythrocyte concentrate, 230 mL fresh frozen plasma (SSP) with a parenteral infusion of terlipressin, somatostatin, esomeprazole and ceftriaxone. Based on laboratory blood count findings, although in the first hour after hematemesis we cannot conclude how much blood volume the patient lost, there was no indication for the transfusion. According to the values of hemodynamic parameters and oxygenation, the patient had no signs of hemorrhagic shock, so there were no indications for the use of blood derivatives.

Four hours after the first hospital episode, hematemesis again occurred, this time patient lost 600 mL of blood. The patient was still in the right state of consciousness, blood pressure was 118/76 mmHg, pulse 86/min, arterial blood saturation 100%. According to hemodynamic laws, the pressure gradient is proportional to flow and resistance (4). Therefore, under the basic pathophysiological law of

hemodynamics we can assume that transfusion has led to increased pressure in the portal circulation and potentiated acute bleeding (9,24). It should be emphasized that fistula between the hepatic artery and the portal vein that was found using CT is an independent risk factor of bleeding from esophageal varices.

In repetitive laboratory findings, a patient treated in General Hospital of Shenyang Military Area has now developed post-hemorrhagic anemia (erythrocytes 2.39×10^{12}/L, hemoglobin 74 g/L, hematocrit 22.1%). Although hemoglobin reduction was now significant and required transfusion, the question is whether patients with portal hypertension should tolerate lower hemoglobin levels of 70 g/L given the fact that transfusion has a potential to increase pressure in the portal circulation? Moreover, this time the patient was not hemodynamically compromised.

In the continuation of the hospitalization, he received a transfusion four times, and after each except last transfusion he was bleeding. After that, the patient had no episodes of hematemesis, and several days later endoscopic therapy (ligation) of esophageal varices was performed, and the general condition of the patient gradually recovered.

According to the opinion and practice of a physician from General Hospital of Shenyang Military Area, transfusion of erythrocyte concentrations is required in patients with acute bleeding from the upper GI tract, as otherwise hypoperfusion can occur. However, tissue hypoperfusion occurs when all hemodynamic compensatory mechanisms are exhausted, i.e., when a hemodynamic failure (shock) occurs. In patients with esophageal varices and acute bleeding, no hemorrhagic shock was observed based on hemodynamic parameters. Thus, the time of transfusion, among other things, also depends on the hemodynamic parameters, i.e., the threatening hemodynamic collapse. The "liberal" approach to blood transfusions in patients suffering from liver cirrhosis with acute bleeding from upper GI tract can cause an increase in a portal pressure and worsen bleeding. The American Association for the Study of Liver Diseases recommends a "restrictive" transfusion strategy in patients with bleeding from esophageal varices. Baveno VI consensus suggests that the limit values for hemoglobin for transfusion should be 70–80 g/L, while Chinese guidelines are slightly more restrictive (hemoglobin threshold for transfusion is 60–70 g/L). In patient treated at the General Hospital of Shenyang Military Area, after the first episode of hematemesis transfusion with erythrocyte was applied at considerably higher hemoglobin values than the recommended one, therefore a "liberal" transfusion strategy was applied which may have potentiated repeated bleeding from the upper GI tract. According to experts, the "liberal" transfusion strategy can be used in patients with cirrhosis of the liver and disrupted coagulograms and thrombocytopenia. In the case of other patients, the general condition of the patient, i.e., signs of hemorrhagic shock (hypotension, tachycardia, consciousness disorder, pallor, coldness, etc.) should be taken when deciding on the transfusion, when without delay and prior to the blood laboratory findings we should start with transfusion support.

Conclusions

Despite the growing body of evidence supporting restrictive transfusion policies, it is important to have in mind that liberal transfusion strategies are not detrimental by itself. In patients with massive blood loss, blood transfusion remains the cornerstone therapy. Unequivocal hemoglobin level for initiation of RBC transfusion as recommended by current guidelines are substantiated by evidence and seems plausible. However, they should be approached with caution due to evidence that the level of hemoglobin does not necessarily represent an accurate quantification of the acute blood volume loss, and its exact value should be taken with a certain reserve when considering transfusion decisions.

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