Editorial

Red blood cell transfusion in the cirrhotic patient with gastrointestinal bleeding

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Acute upper gastrointestinal bleeding (UGIB) is a common medical emergency and blood transfusions are often used in the resuscitation algorithm. The incidence of UGIB ranges from 50 to 150 per 100,000 adults per year (1,2). The most common causes of acute UGIB are peptic ulcer disease and oesophageal or gastric varices (3). Acute variceal bleeding in liver cirrhosis is a life-threatening condition and a serious complication of portal hypertension (4). It is associated with a significantly higher mortality rate compared to non-variceal UGIB, with approximately 30–50% of patients dying within six weeks of the first variceal bleeding episode (4). There are several factors contributing to the increased mortality of acute variceal bleeding including; underlying severity of liver disease, coagulopathy, thrombocytopenia and complications such as renal failure and systemic infection (5). Mandal *et al*. reported that high Child-Pugh score, creatinine and MELD scores were important predictors of mortality (4).

Acute blood loss can result in reduction in circulatory volume, which leads to decreased tissue perfusion and oxygen delivery to tissues. Therefore, red blood cell transfusions can be lifesaving in exsanguinating bleeding (6). Conversely, in patients with portal hypertension, transfusions may cause increased portal pressure or alter coagulation parameters and lead to increased risk of rebleeding and subsequently mortality (3,7). Transfusion is associated with increased hepatic venous pressure gradient (7). The current literature recommends that a restrictive transfusion strategy significantly improved clinical outcomes (survival, re-bleeding, adverse events related to transfusions) (1,2,7-10) and is particularly beneficial in the subgroup of patients with portal hypertension (7).

The exact mechanism as to how liberal blood transfusions cause increased mortality and morbidity is unclear, however there are a few hypotheses that exist. One hypothesis is that liberal blood transfusions have immunomodulatory effects, which could lead to higher risk of acquired infections (10). It has also been postulated that blood transfusions could also cause impaired haemostasis by counteracting the splanchnic vasoconstrictive response caused by hypovolaemia, inducing increased splanchnic blood flow and pressure that cause coagulation abnormalities (7).

Villanueva *et al*. reported that restrictive strategy was associated with a significantly higher probability of survival in the subgroup of patients with cirrhosis and Child-Pugh A or B disease (7). Patients bleeding from oesophageal varices were also noted to have a lower rate of rebleeding and reduced need for rescue therapy (i.e., balloon tamponade or with transjugular intrahepatic portosystemic shunt) in the restrictive strategy group (7). Within the first five days, the liberal transfusion group was noted to have increased portal pressure gradient (7). Furthermore, overall complication rates such as transfusion reactions and cardiac adverse effects (e.g., transfusion related acute lung injury or transfusion associated cardiac overload) were reduced in the restrictive strategy group (7,10). Odutayo *et al*. conducted a meta-analysis that demonstrated a restrictive transfusion strategy was associated with reductions in mortality and rebleeding risk (10).

The recently published article by Bai *et al*. in the *AME*

Medical Journal, was a case report surrounding a patient with Hepatitis B liver cirrhosis who presented with an active UGIB. The patient had a twelve-day history of intermittent haematemesis and melaena. He underwent endoscopic assessment, which confirmed the presence of oesophageal varices with red wale sign and gastric varices but did not undergo endoscopic therapy. A contrast-enhanced computed tomography (CT) scan of his abdomen revealed further complications of portal hypertension: splenomegaly and ascites. There was also a mass in the right hepatic lobe with portal vein tumor thrombosis, a fistula from hepatic artery to portal vein and an ascending colonic wall swelling. This thrombus could have increased portal pressure and contributed to additional increased risk of variceal bleeding and subsequent rebleeding in this case.

On presentation to hospital, he had an episode of haematemesis (approximately 600 mL) and had an initial blood pressure of 110/87, heart rate 87 bpm and haemoglobin was 128 g/L. He was managed as a variceal bleed and received three units of packed red blood cells (PRBC) and fresh frozen plasma 230 mL. He also received terlipressin, somatostatin, esomeprazole and ceftriaxone sodium. Subsequently, he had four further episodes of haematemesis and after each episode he received immediate transfusions of PRBC. In total, he received twelve units of PRBC and 500 mL fresh frozen plasma. His lowest haemoglobin level was 74 g/L. He underwent a second elective endoscopy one month later and varices were treated with band ligation.

Overall, outcomes in variceal bleeding have improved in recent years due to established medical management algorithm as well as advancements in endoscopic therapies and strategies (4). The American Association for the Study of Liver Diseases (AASLD) guideline recommends restricted transfusions of PRBC for patients with variceal bleeding (11). The 2015 UK guideline suggests either excessive or insufficient blood transfusions lead to adverse events. For patients with stable hemodynamics, the target of haemoglobin should be adjusted to 70–80 g/L (12). The medical management of variceal bleeding consists of commencing an intravenous proton pump inhibitor infusion, intravenous infusion of somatostatin analogue and intravenous prophylactic antibiotics for three days (4). Endoscopic interventions for acute variceal bleeding include sclerotherapy, band ligation, balloon tamponade or stenting. Routine endoscopic band ligation also reduces risk of variceal bleeding (4,7).

Bai *et al*. report differing physician opinions at the General Hospital of Shenyang Military Area regarding whether PRBC transfusion should be immediately given to a cirrhotic patient with an active UGIB. Opinions ranged from advocating a more liberal approach in the setting of thrombocytopenia and deranged clotting profile, to awaiting haemoglobin level prior transfusion or correlating urgency of transfusion on the clinical haemodynamic of the patient. Even so, it was also recognised by the physician group that haemoglobin level might be inaccurate in the setting of an active, large volume UGIB.

The recommended timing of blood transfusion in cirrhotic patients with active UGIB remains uncertain. Blood transfusions are generally included in the initial resuscitation of patients presenting with an UGIB. There are no clear guidelines regarding triggers for blood transfusion and amount of transfusions to give patients with an active UGIB. According to the National Institute for Health and Clinical Experience (NICE) UGIB guidelines, the decision to transfuse blood should be based "on the full clinical picture, recognising that over-transfusion may be as damaging as under-transfusion" (13). The Gastroenterological Society of Australia and the American Society for Gastrointestinal Endoscopy do not provide any guidelines on triggers for RBC transfusion in UGIB.

Ultimately, there is a lack of clarity of transfusion guidelines in cirrhotic patients presenting with an acute UGIB, as most of the literature derives from studies of non-variceal UGIB. PRBC transfusion is appropriate therapy in a resuscitation situation, especially if there is an exsanguinating UGIB. Patients in smaller hospitals that do not have immediate access to endoscopy and require transfer to another treatment centre may require more transfusions as a bridge to endoscopic intervention. In these instances, the treating clinician's judgement should dictate management of each individual patient based on their clinical presentation, haemodynamic stability and comorbidities.

Clearly, there is a need for more robust studies of cirrhotic patients presenting with acute UGIB, to formulate recommendations as to appropriate clinical guidelines for PRBC transfusion in this patient cohort.

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