Chapter 7

Red Blood Cell Transfusion Strategy for Upper Gastrointestinal Bleeding

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Abstract

Acute upper gastrointestinal bleeding (UGIB) is a potentially lethal and frequent digestive disease. It is mainly divided into the nonvariceal UGIB and variceal bleeding according to the source of bleeding. Red blood cell transfusion is the core therapeutic option for the management of acute UGIB. In this chapter, we reviewed the primary evidence from meta-analyses and large-scale randomized controlled trials regarding red blood cell transfusion strategy for acute UGIB.

Keywords: red blood cell, transfusion, upper gastrointestinal bleeding, variceal bleeding, peptic ulcer, management, hemoglobin

1. Introduction: Upper gastrointestinal bleeding

1.1. Definition

Traditionally, gastrointestinal bleeding is divided into upper and lower gastrointestinal bleeding according to the site of gastrointestinal tract. Upper gastrointestinal bleeding (UGIB) refers to the occurrence of bleeding above the ligament of Treitz, which is often characterized by hematemesis and/or melena; by contrast, lower gastrointestinal bleeding refers to the occurrence of bleeding below the ligament of Treitz. Currently, some researchers also propose the term "mid gastrointestinal bleeding," which refers to the occurrence of bleeding between the ligament of Treitz and ileocecal valve.

1.2. Incidence

UGIB is one of the most common emergency diseases. The epidemiological data are heterogeneous among regions. In the UK, an audit study identified a total 6750 patients with acute UGIB from 208 hospitals during a 2-month period (May 1–June 30, 2007) [1]. In Wales, there were 22,299 patients with 24,421 admissions for UGIB during an 8-year period (1999–2007) [2]. The hospitalized incidence of UGIB was estimated to be 134 per 100,000 [2]. In Iceland, a prospective population-based study involving 1731 patients undergoing 2058 upper gastrointestinal endoscopies demonstrated that the annual incidence of acute UGIB was 87/100,000 inhabitants [3]. The data were also heterogeneous among periods. In Italy, there were 532 patients with 587 admissions during a 2-year period from 1983 to 1985 and 513 patients with 539 admissions during a 2-year period from 2002 to 2004 [4]. In Crete, Greece, a population-based study found that the annual incidence of acute UGIB was 160/100,000 during a 1-year period from 1998 to 1999 and 95/100,000 during a 1-year period from 2008 to 2009 [5]. In Achaia, Greece, a population-based study found that the annual incidence of acute UGIB was 162.9/100,000 and 108.3/100,000 in1995 and 2005, respectively [6].

1.3. Mortality

UGIB is a potentially lethal disease. Until now, there are lots of data regarding the mortality of patients with UGIB. The mortality is about 10% [1, 2, 7]. A majority of evidence suggests that the mortality is being decreased with time. Loperfido et al. reported that the annual mortality of UGIB decreased from 17.1/100,000 during the period of 1983–1985 to 8.2/100,000 during the period of 2002–2004 [4]. Paspatis et al. also reported that the annual mortality of UGIB decreased from 9/100,000 during the period of 1998–1999 to 6.3/100,000 during the period of 2008–2009 [5]. However, Theocharis et al. found that the overall mortality increased from 3.9% in 1995 to 6.5% in 2005, but no statistically significant difference was found between the two periods [6].

1.4. Causes

Peptic ulcer, which primarily refers to gastric and duodenal ulcer, and gastroesophageal varices, which is primarily caused by liver cirrhosis, are the two most common causes of UGIB [8, 9]. First, the major risk factors of peptic ulcer are recent use of nonsteroidal anti-inflammatory drugs (NSAIDs) and anti-platelet agents, *Helicobacter pylori* infection, Zollinger-Ellison syndrome, and smoking [8, 9]. Aspirin is the most widely used NSAID associated with the development of peptic ulcer, especially in patients with previous history of cardiovascular or cerebrovascular diseases. Second, the major etiologies of gastroesophageal varices include liver cirrhosis, portal vein obstruction, and Budd-Chiari syndrome.

Additional causes of UGIB include malignancy, Mallory-Weiss tears, acute inflammation and erosion of esophageal, gastric, and duodenal mucosa, Dieulafoy's lesions, gastric antral vascular ectasia, and arteriovenous malformations.

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2. Current treatment strategy of UGIB

UGIB is often divided into nonvariceal UGIB and variceal bleeding, because the treatment strategy is greatly different between them.

2.1. Nonvariceal UGIB

Several high-impact consensus and practice guidelines have clearly established the recommendations regarding the management of nonvariceal UGIB. First, in the International Consensus UGIB (ICON-UGIB) conference, the management strategy mainly includes five major sections, as follows: (1) resuscitation, risk assessment, and pre-endoscopy management; (2) endoscopic management; (3) pharmacologic management; (4) nonendoscopic and nonpharmacologic in-hospital management; and (5) post-discharge, acetylsalicylic acid, and NSAIDs [10]. Second, the Asia-Pacific Working Group proposes the consensus statements regarding the management of nonvariceal UGIB as follows: pre-endoscopy prognostic scale, early discharge, use of proton pump inhibitor, timing of endoscopic intervention, endoscopic treatment plus proton pump inhibitor, necessity of second-look endoscopy, angiographic embolization, and use of NSAIDs, aspirin, and/or clopidogrel in specific population [11]. Third, the European Society of Gastrointestinal Endoscopy (ESGE) guideline makes the main recommendations in the following parts: (1) initial patient evaluation and hemodynamic resuscitation; (2) risk stratification; (3) pre-endoscopy management; (4) endoscopic therapy; and (5) post-endoscopy/endoscopic hemostasis management [12].

2.2. Variceal bleeding

Recently, the recommendations regarding the management of variceal bleeding are primarily obtained from the UK practice guideline [13], Baveno VI consensus [14], American Association for the Study of Liver Diseases (AASLD) practice guidance [15], and the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) [16]. In general, the main management strategy is classified as follows: (1) screening for varices; (2) primary prophylaxis of variceal bleeding; (3) treatment of acute variceal bleeding; and (4) secondary prophylaxis of variceal bleeding.

3. Red blood cell transfusion for acute UGIB

3.1. Recommendations from practice guideline and consensus

In nearly all practice guidelines and consensus, a restrictive red blood cell transfusion strategy is proposed.

As for nonvariceal UGIB, the ICON-UGIB recommends that the threshold of initiating red blood cell transfusion should be a hemoglobin level of ≤70 g/L, but does not establish a target

of red blood cell transfusion [10]; the ESGE guideline recommends that the target of red blood cell transfusion should be a hemoglobin level of 70–90 g/L in general population and should be moderately elevated in specific population, such as ischemic cardiovascular diseases [12].

As for variceal bleeding, the UK practice guideline recommends that the target of red blood cell transfusion should be a hemoglobin level of 70–80 g/L in hemodynamically stable patients [13]; the Baveno VI consensus recommends that the target of packed red blood cell transfusion should be a hemoglobin level of 70–80 g/L and should be modified according to the cardiovascular disorders, age, hemodynamic status, and ongoing bleeding [14]; the AASLD practice guidance recommends that the threshold of initiating packed red blood cell transfusion should be a hemoglobin level of ≤70 g/L, and the target should be a hemoglobin level of 70–90 g/L [15].

3.2. Evidence from meta-analyses

Several meta-analyses have been published regarding red blood cell transfusion for the management of UGIB. First, in 2009, Hearnshaw et al. did a Cochrane systematic review and meta-analysis of three trials including 126 patients [17]. The authors suggested no sufficient data regarding the outcomes of red blood cell transfusion for the management of UGIB. Second, in 2010, Jairath et al. updated the Cochrane systematic review [18]. However, no new data were found. The conclusions were unchanged. In 2013, our team did a meta-analysis of four studies and found that restrictive red blood cell transfusion was superior to liberal red blood cell transfusion for the improvement of overall survival, but the risk of rebleeding was similar between the two red blood cell transfusion strategies [19]. However, it should be noted that the characteristics and definitions of restrictive transfusion were heterogeneous among the included studies.

3.3. Evidence from major individual studies

There were two large-scale randomized controlled trials comparing the efficacy and safety of restrictive versus liberal red blood cell transfusion for acute UGIB.

A Spanish, single-center, randomized controlled trial enrolled 921 patients with acute UGIB between 2003 and 2009, in which 461 and 460 patients were assigned to restrictive and liberal red blood cell transfusion groups, respectively [20]. In the restrictive transfusion group, the threshold of initiating red blood cell transfusion was a hemoglobin level of ≤70 g/L, and the target was a hemoglobin level of 70–90 g/L. In the liberal red blood cell transfusion group, the threshold of initiating red blood cell transfusion was a hemoglobin level of ≤90 g/L, and the target was a hemoglobin level of 90–110 g/L. First, the most remarkable finding was that restrictive red blood cell transfusion could significantly decrease the incidence of 6-week death in the overall analysis (5% [23/444] versus 9% [41/445], $P = 0.02$, hazard ratio = 0.55, 95% confidence interval = 0.33–0.92). However, restrictive red blood cell transfusion could not significantly influence the incidence of 6-week death in the subgroup analyses of patients with bleeding from varices (11% [11/93] versus 18% [17/97], $P = 0.18$, hazard ratio = 0.58, 95% confidence interval = 0.27–1.27) or peptic ulcer (3% [7/228] versus 5% [11/209], $P = 0.26$, hazard

ratio = 0.70, 95% confidence interval = 0.26–1.25). Second, restrictive red blood cell transfusion could significantly decrease the incidence of further bleeding in the overall analysis (10% [45/444] versus 16% [71/445], *P* = 0.01, hazard ratio = 0.62, 95% confidence interval = 0.43–0.91). However, restrictive red blood cell transfusion could not significantly influence the incidence of further bleeding in the subgroup analyses of patients with bleeding from varices (11% [10/93] versus 22% [21/97], *P* = 0.05, hazard ratio = 0.50, 95% confidence interval = 0.23–0.99) or peptic ulcer (10% [23/228] versus 16% [33/209], *P* = 0.09, hazard ratio = 0.63, 95% confidence interval = 0.37–1.07).

A UK multi-center pragmatic, open-label, cluster randomized trial enrolled 936 patients with acute UGIB between 2012 and 2013, in which 403 and 533 patients were assigned to restrictive and liberal red blood cell transfusion groups, respectively [21]. In the restrictive transfusion group, the threshold of initiating red blood cell transfusion was a hemoglobin level of ≤80 g/L, and the target was a hemoglobin level of 80–100 g/L. In the liberal red blood cell transfusion group, the threshold of initiating red blood cell transfusion was a hemoglobin level of ≤100 g/L, and the target was a hemoglobin level of 100–120 g/L. Neither 28-day mortality (5% [14/257] versus 7% [25/383]) nor further bleeding (5% [13/257] versus 9% [31/383]) was significantly decreased by the restrictive transfusion strategy. No subgroup analyses according to the source of bleeding were available.

3.4. Real-world practice

Despite the restrictive red blood cell transfusion strategy is clearly recommended by the major practice guidelines and consensus, not all clinicians fulfilled this policy in clinical practice. A UK survey of six clinical scenarios regarding red blood cell transfusion triggers for acute UGIB in different clinical conditions was conducted in 815 clinicians [22]. A majority of clinicians would like to choose a red blood cell transfusion trigger of 60–100 g/L, and only a minority of clinicians agreed to choose a red blood cell transfusion trigger of ≥100 g/L. Compared with the surgeons, the physicians preferred to choose a higher red blood cell transfusion trigger. A Canadian survey of seven clinical vignettes regarding red blood cell transfusion threshold for acute UGIB in different clinical conditions was conducted in 203 clinicians [23]. The red blood cell transfusion threshold was a mean hemoglobin level of 71 and 86.7 g/L in hemodynamically stable and unstable patients, respectively; a mean hemoglobin level of 84, 74.4, and 71 g/L in patients with coronary artery disease, with liver cirrhosis, and without previous disease history, respectively.

4. Conclusions

Acute UGIB is a lethal and frequent digestive disease. A restrictive red blood cell transfusion has been clearly recommended by the practice guidelines and consensus. Generally, the threshold for initiating red blood cell transfusion should be often a hemoglobin level of ≤70 g/L, and the target of red blood cell transfusion should be a hemoglobin level of 70–80 or 70–90 g/L (**Table 1**). However, based on two large-scale randomized controlled trials, we could

Guideline or consensus	Nonvariceal UGIB	Variceal UGIB
International Consensus UGIB (ICON-UGIB)	Hemoglobin ≤ 70 g/L	
European Society of Gastrointestinal Endoscopy (ESGE)	Hemoglobin 70–90 g/L	
United Kingdom practice guideline		Hemoglobin 70–80 g/L
Baveno VI consensus		Hemoglobin 70–80 g/L
American Association for the Study of Liver Diseases practice guidance		Hemoglobin ≤ 70 g/L

Table 1. Current recommendations from guideline and consensus regarding red blood cell transfusion.

not establish any strong recommendations regarding restrictive red blood cell transfusion in individual patients with variceal bleeding or nonvariceal UGIB. Additionally, in clinical practice, not all clinicians completely fulfilled a restrictive red blood cell transfusion strategy.

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