Best Practice & Research Clinical Gastroenterology 42-43 (2019) 101600

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: https://ees.elsevier.com/ybega/default.asp

The optimal use of blood components in the management of gastrointestinal bleeding

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ARTICLE INFO

Article history:
Received 28 January 2019
Accepted 14 February 2019

Keywords:
Gastrointestinal bleeding
Transfusion
Blood components
Blood products
GI bleeding
UGI bleeding
Variceal bleeding

ABSTRACT

Acute gastrointestinal bleeding accounts for 5,000 deaths per annum in the UK and is the second-most common indication for transfusion of blood components. Transfusion of blood components is integral to management of these patients. Recent years have seen an expansion in the evidence base for their use in this population and this review aims to provide up-to-date guidance on the use of red cells, plasma, platelets, sources of concentrated fibrinogen and adjuncts such as antifibrinolytic agents in patients with acute gastrointestinal haemorrhage. Key considerations include whether or not it is appropriate to extrapolate from studies in trauma patients to the GI bleeding population, whether restrictive red cell transfusion is appropriate for all patients and whether the presence or absence of liver disease has implications for our transfusion practice. Clinical evidence now favours restrictive transfusion of red blood cells in the haemodynamically stable bleeding patient, but there remain significant evidence gaps concerning the use of plasma, platelets and adjunctive measures.

Introduction

Acute gastrointestinal bleeding is the second-most common indication for transfusion of blood products in the UK, and is a cause of 5,000 deaths per annum [1]. This review aims to provide up-to-date guidance on the use of red cells, plasma, platelets, sources of concentrated fibrinogen and adjuncts such as antifibrinolytic agents in patients with acute gastrointestinal haemorrhage. Key considerations include the validity of extrapolation from the trauma literature to gastrointestinal bleeding, and considerations related to the comorbidities of the gastrointestinal bleeding population, namely cardiovascular disease and liver cirrhosis.

Gastrointestinal bleeding can be divided anatomically into upper and lower gastrointestinal bleeding, based on the relation of the bleeding site to the ligament of Treitz. The aetiology, epidemiology and management of these diseases are distinct. Bleeding from the upper gastrointestinal tract accounts for the majority of GI bleeding seen in UK hospitals and is usually managed by hospital physicians. The common causes of this presentation are peptic ulcer disease, oesophagitis, malignancy of the GI tract and oesophageal or gastric varices [2]. Acute lower gastrointestinal bleeding is typically caused by complications of diverticular disease, and benign ano-rectal diseases [3]. These patients typically present to and are managed by surgeons in the UK, although practice varies on other continents.

The initial management of gastrointestinal bleeding involves resuscitation with fluids and transfusion, pharmacological measures and correction of coagulopathy in order to allow time for definitive surgical or endoscopic treatment directed at the site of bleeding. Recent years have seen a paradigm shift in the practice of red-cell transfusion in GI bleeding, although major uncertainties still surround the use of other blood products including plasma, platelets and concentrated sources of fibrinogen.

In addition to anatomical distinctions between upper and lower GI bleeding, a distinction may also be drawn based on the haemodynamic status of the patient between those presenting with haemodynamic compromise and/or features of hypoperfusion and

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https://doi.org/10.1016/j.bpg.2019.02.002
1521-6918/

those presenting with no haemodynamic compromise. Guidelines for haemodynamically unstable patients often extrapolate directly from research in bleeding major trauma patients - a patient population distinct from the population of patients with acute GI bleeding in their age, co-morbidities and physiological state.

Transfusion in the haemodynamically unstable patient

A small but significant proportion of patients with gastrointestinal bleeding present to hospital with haemodynamic instability and/or features of hypoperfusion. The 2007 UK audit of upper gastrointestinal bleeding remains one of the largest observational studies of upper gastrointestinal bleeding. Data including demographics, physiological and laboratory parameters, diagnosis, and in-hospital outcomes from 6750 patients were collected prospectively from 208 hospitals over 2 months in 2007. This study reported that 13.8% of patients with AUGIB had a systolic blood pressure of less than 100 mmHg at presentation [2]. A subsequent audit of lower GI bleeding in the UK conducted with identical methodology collected data from 2528 patients across 139 hospitals in the UK over 2 months in 2015. 2.3% of these LGIB patients presented with haemodynamic shock (defined as HR > 100 and sBP <100) [3].

Shock at presentation is an adverse prognostic marker [4] and the priorities in these patients are resuscitation (with intravenous fluids, blood products and occasionally vasopressors) and definitive control of the bleeding with emergent endoscopy, radiological intervention or surgery. Haemodynamic parameters, venous lactate, mixed venous oxygen saturations and urine output may be used as surrogate markers of tissue oxygen delivery in these patients. In the actively bleeding patient at initial presentation, haemoglobin and haematocrit are unreliable markers of severity of haemorrhage due to rapid volume depletion and/or vigorous resuscitation with intravenous crystalloids or colloids [5].

National guidelines [6,7] recommend resuscitation of the unstable patient with gastrointestinal bleeding according to major haemorrhage protocols incorporating red cells and plasma in a ratio of 1:1 or 1:2, and platelets and fibrinogen in accordance with laboratory parameters. The evidence-base for these crystalloid-restrictive, empiric transfusion algorithms is largely derived from studies of bleeding in major trauma. Several large retrospective analyses indicate that large volume infusion of crystalloids is associated with increased in-hospital mortality in trauma patients [8–11], and retrospective analyses have indicated that higher ratios of plasma to red cells are associated with improved outcomes in trauma [12,13]. However these findings are susceptible to residual confounding by illness severity as well as immortal time bias, and there is a lack of high-quality prospective randomised evidence supporting empiric transfusion. Despite this lack of high-quality evidence there has a been a significant move in trauma resuscitation towards “damage control resuscitation” or “haemostatic resuscitation” - using plasma, platelets and red cells in combination as a resuscitation fluid in ratios approximating 1:1:1, and this is informing practice in managing patients with massive gastrointestinal bleeding.

The physiological basis for this empiric-transfusion strategy is that it represents a close approximation of reconstituted whole blood, and is hypothesised to prevent and treat the early coagulopathy of trauma. This multi-factorial coagulopathy is evident in over 25% of trauma patients at the time of arrival in hospital, and is hypothesised to be due to a combination of consumptive coagulopathy due to tissue factor release in severe trauma, compounded by hypothermia, acidosis and dilutional effects related to resuscitation [14]. Coagulopathy is also common in patients with gastrointestinal bleeding, and the 2007 audit demonstrated that 16.4% of upper GI bleeding patients had an INR of greater than 1.5 on presentation, 46% of whom were taking oral anticoagulation prior to presentation [2]. A secondary analysis of this UK audit demonstrated an increased incidence of haemodynamic compromise and higher odds of mortality amongst those patients with coagulopathy at presentation with nonvariceal upper gastrointestinal haemorrhage [15]. In the case of lower GI bleeding, 10.6% of patients in the National audit presented with an INR of >1.5, of whom 82% were taking either warfarin or a DOAC, 1% had liver disease and one patient had a congenital bleeding disorder. The aetiology of coagulopathy in GI bleeding is distinct from that in trauma. In the case of GI bleeding, the commonest causes of coagulopathy are oral anticoagulants and liver cirrhosis. The coagulopathy of cirrhosis is a complex combined deficiency of both pro-thrombotic and anticoagulant factors [16,17], thrombocytopaenia, platelet dysfunction and fibrinolysis. Most procoagulant factors are decreased in end-stage liver disease, however factor VIII and von-Willebrand factor are typically elevated, and most anticoagulant factors are also deficient. This state is often considered a “rebalanced” haemostasis, as the in vitro thrombin generation capacity of plasma from cirrhotic patients is found to be preserved, often even demonstrating hypercoagulability [18], and some parameters on viscoelastic testing may be normal [19]. It is also well-attested that laboratory haemostatic testing responds unpredictably to transfusion of coagulation factors in these patients, and bleeding risk is often not significantly altered by transfusion of blood components [20,21]. The extent to which practices primarily addressed at the coagulopathy of trauma can help address the coagulopathy of chronic liver disease remains therefore unclear.

A major trial relevant to the use of plasma in trauma is the PROPRR randomised trial [22]. This was a multi-site pragmatic randomised controlled trial which randomised patients with severe polytrauma and anticipation of need for massive transfusion to standard care plus transfusion of plasma, platelets and red cells in a 1:1:1 ratio or standard care plus transfusion of plasma, platelets and red cells in a 1:1:2 ratio. 680 patients were recruited at 12 sites in North America. There was no significant effect on the primary outcomes (mortality at 24 h and at 30 days), but haemostasis was achieved in a higher proportion of those in the 1:1:1 group (86% vs 78%, $p = 0.006$). Significantly, despite higher volumes of plasma and platelets being transfused in the 1:1:1 group, there was no difference between the groups in the number of transfusion reactions.

The PAMPer trial was a cluster-randomised study which randomised trauma patients at risk of haemorrhagic shock in the pre-hospital setting to receive either standard care or standard care plus 2 units of thawed plasma whilst on air-transport to the trauma centre [23]. 523 patients were enrolled. The primary outcome was mortality at 30 days. Those allocated to receive plasma had a 9.8% (95% CI, 1%–18.6%) lower mortality at 30 days, an effect which persisted after adjustment for volume of crystalloid transfused and volume of red cells transfused (adjusted OR for mortality at 30 days 0.61; 95% CI, 0.40–0.91). Despite theoretical concerns that transfusion of higher volumes of plasma would result in a greater number of transfusion reactions or an increased incidence of nosocomial infections, no such effects were observed. This study also reported prothrombin time as a secondary outcome - those allocated to receive plasma had a significantly lower prothrombin time ratio on arrival at hospital (1.2 vs 1.3, $p < 0.001$). Interpretation of this study however is limited by non-standardised fluid management in the standard-care group, and significant differences in red cell and crystalloid use between groups.

It is controversial whether or not these findings should be extrapolated to gastrointestinal bleeding. The population of trauma patients are typically young, healthy, and not on anticoagulant or antiplatelet medication, whereas the population of patients with

upper GI bleeding are older, more comorbid and taking more medications. For example, the 2007 upper GI bleeding audit in the United Kingdom reported that the median age of patients presenting with acute upper GI haemorrhage was 68 years, 53% had at least one major comorbidity, 28% were taking aspirin and 7% were taking a vitamin K antagonist [2]. In the lower GI bleeding audit, the median age was 74, 79.1% had at least one comorbidity and 42.8% were taking either an antiplatelet or anticoagulant medication [3]. The population in the PAMPer trial had a median age of 45, 8% were taking any antiplatelet medication and 3% were taking a vitamin K antagonist. Given these differences, it is plausible to think that patients with upper GI bleeding may be more susceptible to circulatory overload and other complications of transfusion than the trauma population, but that remains to be borne out in randomised studies of unstable patients with GI haemorrhage. In addition, patients with liver cirrhosis, portal hypertension and gastrointestinal bleeding are particularly susceptible to volume overload and further exacerbation of portal pressures. As it stands, most national and international guidelines are in agreement that the haemodynamically unstable patient with gastrointestinal bleeding should be resuscitated with blood components in accordance with a fixed-ratio major haemorrhage protocol.

Transfusion in the haemodynamically stable patient

A greater proportion of patients with gastrointestinal bleeding present without shock or haemodynamic compromise. In these patients transfusion is typically guided by laboratory parameters. There has been considerable debate surrounding transfusion thresholds for red cells, and the benefits of plasma or sources of concentrated fibrinogen in these patients, with moves towards restrictive red cell transfusion strategies over recent years [1,24]. There are many outstanding questions in this area, particularly surrounding whether patients with differing aetiologies to their bleeding respond differently to different transfusion strategies, or whether the presence of cardiovascular disease or cirrhosis modulates the risks or benefits of certain transfusion strategies.

Red cell transfusion

The aim of red cell transfusion is to increase the oxygen-carrying capacity of the blood in order to augment tissue oxygen delivery. In most cases of acute gastrointestinal bleeding, red cells are transfused not as a resuscitative measure but rather as a treatment for anaemia. In the 2007 audit of upper GI bleeding 43% of patients received a red cell transfusion, with only 23.5% of these being transfused for hypotension. The majority of the remainder were transfused for anaemia, however 5% of patients receiving red cells in this audit did not have a clinical indication for transfusion – at the time deemed to be haemodynamic instability or a haemoglobin of <10 g/dL. In the 2015 audit of lower GI bleeding in the UK, 26.7% of patients received a red cell transfusion and the investigators suggested that as many as 70% of these transfusions were inappropriate (using a restrictive threshold of 7 g/dL to determine appropriateness). As a biological product, red cell transfusion is associated with potential complications, including haemolytic reactions, circulatory overload, transfusion-related acute lung injury and transmission of blood-borne infections. Randomised studies and meta-analyses have shown that in critically ill patients, restrictive transfusion practices are associated with fewer transfusions of red cells without patient harm [25–27] and in recent years, randomised controlled trials have also evaluated this hypothesis in acute gastrointestinal bleeding.

Villanueva and colleagues conducted a seminal randomised trial of restrictive (threshold of 7 g/dL) versus liberal (threshold of 9 g/dL) transfusion strategies in acute upper gastrointestinal bleeding [28]. Patients presenting to a single centre in Barcelona were eligible if they had haematemesis, melaena or a bloody nasogastric aspirate and were excluded if they had exsanguinating haemorrhage, a Rockall score of 0 with Hb > 12 g/dL, significant current cardiovascular disease or transfusion in the previous 90 days. 921 patients were randomised. Investigators observed a significant reduction in mortality at 6 weeks in the restrictive group (HR 0.55; 95% CI, 0.33–0.92) with a significantly lower rate of transfusion reactions. The generalisability of this trial has been called into question for several reasons however. The patient cohort was not representative of what is observed in most hospitals, with a very high proportion of variceal haemorrhages (24% vs 11% in the 2007 UK audit), and patients had very rapid access to definitive therapies (100% had endoscopy within 6 h). The exclusion of patients with significant current cardiovascular disease (acute coronary syndrome, peripheral vascular disease or stroke or transient ischaemic attack) also limits the external validity of this study.

The TRIGGER trial was a cluster-randomised, open-label feasibility study comparing liberal transfusion strategies (threshold 10 g/dL) with restrictive transfusion strategy (threshold 8 g/dL) in acute upper GI bleeding [29]. Patients were eligible if they had either haematemesis or melaena and the only exclusion criterion was exsanguinating haemorrhage. 936 patients were enrolled. Although a feasibility study, and not powered for clinical outcomes, there did not appear to be any harm associated with restrictive transfusion in this study. Of note, there was significantly poorer adherence to the liberal (83% adherence) transfusion protocol than the restrictive (96% adherence) protocol in the TRIGGER study, perhaps indicating that clinicians were already engaged in restrictive practices and reluctant to over-transfuse in an open-label study.

These trials provided 93% of the participant data for a recent meta-analysis of randomised controlled trials of restrictive vs liberal transfusion in GI bleeding [30]. Odutayo and colleagues conducted a study-level meta-analysis of five randomised trials demonstrating a significant reduction in all-cause mortality (RR 0.65, 95% CI 0.44–0.97) and rebleeding (RR 0.58, 95% CI 0.40–0.84) with restrictive transfusion practices with no increase in ischaemic events.

National guidelines have now adopted restrictive transfusion thresholds [6,7]. Significant questions do remain unanswered. None of the published randomised studies is powered to detect differential effects in patients with different aetiologies of bleeding. The pathophysiology of variceal bleeding is distinct from bleeding related to peptic ulcer disease or oesophagitis. Transfusion of blood components occurs more frequently in patients with liver cirrhosis [31] and transfusion of red cells is likely to modulate this physiology in differing ways. Villanueva and colleagues demonstrated a higher portal pressure gradient in cirrhotic patients allocated to liberal transfusion versus those in the restrictive transfusion groups, and more patients in the liberal transfusion group required transjugular intrahepatic portosystemic shunt (TIPS) procedures due to complications of portal hypertension [28]. This illustrates a potential mechanism by which transfusion could confer additional harm in patients with cirrhosis.

A further key consideration is how the effect of transfusion may be modulated by the presence of ischaemic heart disease. 20.9% of patients in the 2007 UGIB audit and 10.9% of patients in the 2015 LGIB audit had a documented history of ischaemic heart disease. There is little evidence on transfusion thresholds specifically in patients with established cardiovascular disease. A large randomised trial in 2015 of 2003 patients undergoing cardiac surgery demonstrated an increased mortality risk associated with restrictive transfusion [32]. A systematic review and meta-analysis of

restrictive versus liberal red cell transfusion trials which either included patients with established cardiovascular disease as the entire population or as part of the population, demonstrated no overall effect on mortality but an increase in the risk of acute coronary syndromes associated with restrictive transfusion [33]. A more recent, larger trial randomised over 5000 moderate to high risk patients undergoing cardiac surgery to either restrictive or liberal transfusion strategies and demonstrated that restrictive transfusion was non-inferior with a composite primary outcome of death, myocardial infarction, stroke or renal failure [34]. How this knowledge may be applied to gastrointestinal bleeding is not clear.

Plasma

The role for plasma transfusion in patients with GI haemorrhage and haemodynamic instability has been discussed above. However most plasma transfusions are not given as part of resuscitation, but are used either to prevent bleeding or treat bleeding, often directed by laboratory coagulation parameters. UK NICE guidance on upper GI bleeding recommends transfusion of frozen plasma in actively bleeding patients if the INR is > 1.5, and coagulopathy is independently associated with mortality in acute upper GI bleeding [15]. The national audit of Upper GI bleeding in 2007 reported that 15% of patients had an INR of >1.5 at presentation, of whom around half received fresh frozen plasma. The cause of coagulopathy in the majority of these cases was synthetic liver dysfunction, followed by warfarin use. This is in contrast to patients with lower GI bleeding, amongst whom warfarin was the most common cause of coagulopathy with hepatic dysfunction accounting for only 1%.

In the case of coagulopathy caused by oral anticoagulant medication, prothrombin complex concentrate is most appropriate for reversing the effects of vitamin K antagonists. The evidence for the use of blood components to reverse the anticoagulant effects of DOACs is not of a high quality. Evidence from animal [35] and healthy human [36] models suggest that prothrombin complex concentrates may be effective at reversing DOAC induced coagulopathy. Plasma is often used in the reversal of DOACs, but the evidence for this practice is not clear. Dabigatran has a licensed reversal agent for use in severe haemorrhage – idarucizumab.

The evidence base for using FFP to treat coagulopathy associated with impaired hepatic synthetic function is poor. Coagulopathy in liver disease is complex, and many of these patients can have normal parameters on viscoelastic testing and thrombin generation assays despite prolonged prothrombin times, indicating that clot formation may not be severely impaired [16,19]. Although traditionally viewed as a disorder of impaired haemostasis it is probably more accurate to consider the coagulopathy of liver disease as a "rebalanced haemostasis", as it can be associated with thrombotic as well as haemorrhagic outcomes. There is limited evidence to suggest that raised INR in these patients is associated with increased bleeding risk [20,21], and limited evidence to suggest that treatment with FFP either improves coagulation parameters or reduces bleeding risk in vivo.

Platelets

Thrombocytopaenia is rare amongst patients with acute gastrointestinal haemorrhage, affecting only 5.2% of patients with upper GI bleeding [2]. Platelet numbers are typically reduced in cirrhosis and their function may be altered, but a complex balance of elevated von Willebrand factor and reduced ADAMTS13 activity in cirrhotic patients may in fact render primary haemostasis relatively preserved [37], and platelet count does not correlate with bleeding risk in these patients [38].

Current NICE guidelines are to transfuse platelets if the platelet count is less than 50 and the patient is actively bleeding. In the national audit in 2007, 58% of platelet transfusions were in accordance with this guidance. 61% of patients with a platelet count less than 50 did not receive a platelet transfusion. The indications for the remaining 42% of platelet transfusions are not clear – it is possible that they are being administered as an effort to reverse the effect of antiplatelet medication. Overall, 2.8% of patients received a platelet transfusion in the audit, but significantly higher proportion of patients with variceal haemorrhage (14%) received platelet transfusions [31].

There is no randomised evidence to support a particular transfusion threshold for platelets in GI bleeding, and the existing guidance is based on expert opinion and extrapolations from platelet transfusions in patients with haematological malignancies. Historically, much of the literature on platelet transfusions has been undertaken in patients with haematological malignancies, and has supported a restrictive transfusion strategy. Recent randomised studies outside that field in Dengue fever [39] and preterm neonates [40] have confirmed the safety of restrictive platelet transfusion thresholds. Neither of these trials demonstrated an increased bleeding risk associated with restrictive use of platelets.

Platelet transfusions are often administered to reverse the effects of antiplatelet medications. A randomised controlled trial of platelet transfusion to reverse the effect of antiplatelet medication in intracranial haemorrhage [41] found increased risk of death or dependence at three months in the patients receiving platelets. There is a paucity of evidence for this practice in the setting of gastrointestinal bleeding. A case-control study of gastro-intestinal bleeding found that platelet transfusion in patients on antiplatelet medication at the time of bleeding did not improve outcomes [42]. This was a single-centre study in the United States - 204 cases of GI bleeding in patients on antiplatelet medication who received platelet transfusion were matched for age, sex and GI bleed location with 204 controls who did not receive a platelet transfusion. Multivariate analysis (adjusted for haemodynamic parameters, presence of a coronary stent, ICU admission and anaemia) demonstrated an increased risk of death associated with platelet transfusion (adjusted OR 5.57, 95% CI: 1.52–27.1). This may be related to the long half-life of circulating platelets and it remains to be seen whether such an effect will be observed in randomised studies.

An area of future interest is the use of desmopressin to treat platelet dysfunction, including that caused by antiplatelet medication. A recent meta-analysis of four randomised trials concluded that desmopressin resulted in lower rates of red cell transfusion and lower blood loss in platelet dysfunction in cardiac surgery, but noted that the standard of the evidence was low [43].

Thrombocytopaenia is less common in lower GI bleeding (1.3%), as would be expected given the lower incidence of hepatic dysfunction amongst these patients [1] although platelet function may be impaired due the high prevalence of antiplatelet use amongst these patients.

Sources of concentrated fibrinogen

There is little evidence supporting transfusion of fibrinogen in gastrointestinal bleeding. Current NICE guidance is to transfuse cryoprecipitate if the plasma fibrinogen concentration remains <1.5 g/L despite use of fresh frozen plasma. 1.3% of patients in the 2007 audit received cryoprecipitate, indicating that this is a very rare intervention.

There are ongoing trials investigating the role of early cryoprecipitate in trauma. CRYOSTAT-1 demonstrated the feasibility of early delivery of cryoprecipitate in trauma [44] and CRYOSTAT-2 is now randomizing patients to cryoprecipitate + standard care or

placebo + standard care with a primary outcome of all-cause mortality at 28 days. There is no randomised literature directly comparing the effects of different fibrinogen sources (cryoprecipitate vs fibrinogen concentrate) in acutely bleeding patients.

Of particular interest in gastrointestinal bleeding is the fact that hypofibrinogenaemia has been shown to independently associate with bleeding risk in patients with cirrhosis [45]. Whether correcting this abnormality will ameliorate bleeding risk remains to be seen.

Antifibrinolytics

The use of antifibrinolytics in life-threatening bleeding has significantly influenced the management of severe trauma and post-partum haemorrhage after the publication of two of the largest trials in the study of bleeding: CRASH-2 and WOMAN [46,47]. Both of these trials demonstrated a significant reduction in mortality associated with the use of tranexamic acid in addition to standard care in trauma and post-partum haemorrhage respectively. A randomised, placebo-controlled trial (HALT-IT) in of tranexamic acid in gastrointestinal bleeding is currently recruiting [48]. Current NICE guidance does not mention antifibrinolytic agents [7], and the European Society of Gastroenterology Guidelines from 2015 do not recommend the use of antifibrinolytic agents [49].

In the context of chronic liver disease, various participants in the fibrinolysis pathway are known to be dysregulated, chiefly a deficiency of TAFI (thrombin-activated fibrinolysis inhibitor) [50,51]. It will be illuminating to see therefore whether anti-fibrinolytics have a differential effect in patients with advanced liver disease.

Recombinant factor VIIa

Recombinant factor VIIa is licensed for use in haemophilia with factor inhibitors. It is used widely for off-label indications and is regarded as a rescue therapy when all other interventions to control bleeding have failed. NICE guidance recommends it be used in gastrointestinal bleeding only when all other measures have failed. There have been two randomised controlled trials of recombinant factor VIIa in upper gastrointestinal bleeding – specifically in cirrhotic patients. The first trial randomised 245 patients with liver cirrhosis (Child-Pugh A, B or C) and either variceal (66%) or non-variceal bleeding to receive standard care plus 8 doses of recombinant factor VIIa or standard care plus placebo [52]. No effect was demonstrated in the primary composite outcome of haemostasis, prevention of rebleeding and 5 day mortality. The second trial randomised 256 patients with advanced cirrhosis (Child-Pugh B or C) and variceal haemorrhage to receive standard care plus placebo, or standard care plus one of 2 different doses of recombinant factor VIIa [53]. This trial did not demonstrate an improvement in the same composite primary outcome with use of recombinant factor VIIa. An individual patient data meta-analysis of these trials demonstrated an improvement in the composite outcome with recombinant factor VIIa when only patients with variceal bleeding and Child-Pugh > 8 were included (OR: 0.53, 95% CI: 0.29–0.97) [54]. In short, there is a possibility that recombinant factor VIIa may be efficacious in variceal bleeding in advanced cirrhosis, but it remains to be borne out in a well-designed clinical trial.

Summary

Transfusion of blood components in the management of gastrointestinal bleeding has two main purposes:

1. As a resuscitative measure in patients with severe bleeding in order to buy time for definitive treatment directed at the site of bleeding
2. In order to prevent and treat anaemia and rebleeding.

In the first case, practice and guidelines are changing in line with that seen in the field of trauma – fixed-ratio empiric transfusion. There is insufficient evidence at present to say whether this is an appropriate strategy in gastrointestinal bleeding, and it is important that clinicians bear in mind the differing demographics and physiology of these two populations. It is especially important to consider the specific case of the cirrhotic patient with gastrointestinal bleeding. Portal hypertension and coagulopathy create a specific physiological milieu which may respond differently to empiric transfusion than a bleeding trauma patient. In the Villanueva trial investigators demonstrated an increased portal pressure following liberal transfusion, and observational studies have demonstrated that coagulopathy as measured by laboratory parameters in these patients may be a poor indicator of bleeding risk.

The evidence-base for transfusion in the stable patient is clearer, and favours transfusion of red blood cells with a restrictive threshold. An outstanding question in this area is whether this strategy remains appropriate in patients with significant cardiovascular disease, with research in other fields suggesting that restrictive transfusion in patients with significant cardiovascular disease may be associated with increased morbidity and mortality.

Although there is clear national guidance surrounding the use of platelets and plasma in the bleeding patient, there is a lack of specific evidence from the GI bleeding population to support these recommendations. A specific consideration is the coagulopathy of advanced liver disease, which although associated with deranged laboratory measures of coagulation, may not be associated with increased bleeding risks and my in respond unpredictably to transfusion of blood components. Future work may establish a role for novel tests of coagulation including thrombin generation assays and visco-elastic testing in the management of these patients.

Research agenda

- Further clinical research is necessary to establish the safety and efficacy of empiric fixed-ratio transfusion in unstable GI bleeding. Such prospective cohort studies or randomised trials should be powered to detect differential effects in patients with or without cirrhosis.
- Further laboratory research is required to identify novel tests which can accurately predict bleeding risk in patients with cirrhosis, as standard laboratory haemostatic testing correlates poorly with bleeding risk amongst these patients.

Practice points

- The limited available evidence indicates that patients presenting with gastrointestinal haemorrhage and haemodynamic instability should be resuscitated with blood components according to local major haemorrhage protocols including fixed-ratio empiric transfusion.
- In the haemodynamically stable patient with gastrointestinal bleeding, the evidence favours red cell transfusion with a restrictive haemoglobin threshold.
- Current guidelines recommend transfusion of plasma and platelets according to laboratory parameters, but evidence to support this practice in gastrointestinal bleeding is lacking.
- Transfusion should be tailored to the individual patient, including careful consideration of comorbidities including

cardiovascular disease and cirrhosis, and the potential adverse effects of over-transfusion in patients with these co-morbidities.

Conflicts of interest

KD, SS and VJ have no relevant conflicts of interest to report.

Acknowledgements

None.

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