Haematological problems in intensive care

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Abstract

Anaemia is common in the ICU patient and is usually due to the interplay between many different factors. Although often this can be safely managed conservatively, red cell transfusion is commonly required. Patients who refuse blood products and patients with critical bleeding pose a particular management challenge. Coagulopathy is also frequently encountered in ICU. It is critical to evaluate the causes and bleeding risk in such patients, as this will determine the subsequent management. In the stable patient it is often not necessary to correct the coagulopathy. Heparin resistance is failure to reach therapeutic targets using heparin as measured by commonly used laboratory tests. It is influenced by a number of factors relating to the nature of heparin and its mode of action and may result in failure to achieve intended clinical outcomes. Heparin-induced thrombocytopenia (HIT) is an immune-mediated syndrome caused by heparin-dependent antibodies leading to platelet activation and subsequent thrombocytopenia. Awareness and prompt treatment are essential to prevent morbidity and mortality resulting from the development of thrombosis, which can occur in half of patients with HIT.

Keywords Anaemia; antithrombin; coagulopathy; heparin resistance; heparin-induced thrombocytopenia; massive transfusion

Royal College of Anaesthetists CPD Matrix: 2C00

Learning objectives

After reading this article, you should be able to:

- understand issues relating to the management of anaemia in stable and bleeding ICU patients
- understand issues relating to the management of coagulopathy in stable and bleeding ICU patients
- list factors contributing to heparin resistance
- assess the probability of HIT in thrombocytopenic patients
- understand the pathophysiology and principles of management of HIT

Anaemia and transfusion

Anaemia is almost universal in ICU patients. It can be the result of a number of factors including acute blood loss, long-term phlebotomy, anaemia of inflammation, suppressed erythropoiesis due to illness, the effects of drugs and renal impairment, as well as pre-existing haematinic deficiencies and other conditions. Often, many of these exist in the same patient and it can be difficult to tease out the relative impact of each individual factor. Some can be easily remedied, but most rely on the slow recovery from acute illness.

While the patient is being treated and the factors contributing to the anaemia are being addressed, the anaemia itself may require treatment with red cell transfusions. A conservative transfusion strategy in the stable ICU patient has been widely adopted since the publication of the trial of transfusion requirements in critical care (TRICC) in 1999. This was a multicentre randomized controlled trial (RCT) showing that a conservative transfusion strategy (Hb 70 g/L as trigger for transfusion) is at least as effective as a liberal one (Hb 100 g/L as trigger for transfusion) in stable, non-bleeding critical care patients.[1] Two recent RCTs comparing a more restrictive versus liberal transfusion approach in patients post cardiac surgery and elderly patients with cardiac risk factors post hip fracture surgery also demonstrate safety using a restrictive transfusion approach.[2,3] Clearly, however, the decision of when to transfuse is influenced by a number of different factors and needs to be evaluated in each patient.

The management of anaemia in patients who refuse blood products, such as Jehovah's Witnesses, poses a particular challenge. The focus in such patients is on minimizing iatrogenic blood loss through limiting phlebotomy and optimizing erythropoiesis through the replacement of haematinics and the use of erythropoietic agents. Most institutions have a guideline as well as a liaison officer to aid clinicians in these situations. However, it is important to clarify with individual patients exactly what interventions they will or will not accept. Anecdotal and case reports of patients who refuse blood products suggest that acute anaemia can be well tolerated.[4]

Massive transfusion in trauma patients

The most commonly used definition of massive transfusion is replacement of one blood volume in 24 hours. Given this is somewhat retrospective, a more helpful definition may be replacement of half a blood volume in 4 hours. Regardless of the definition used, it is important to recognize critical bleeding early and act promptly to both limit blood loss and resuscitate the patient appropriately to maintain adequate tissue perfusion, thereby avoiding the development of coagulopathy, hypothermia and acidosis.

As a relatively recent initiative, many centres have developed massive transfusion guidelines which include dose, timing and ratios of blood products transfused and advocate a team approach to the management of trauma patients with critical bleeding involving the treating clinician, blood bank staff and transfusion specialist. Such initiatives have a limited evidence base but the aim is to reduce blood product usage and improve survival in trauma patients with critical bleeding.

There is much ongoing debate on optimal ratios of blood products to be used. Recent concentrated experience from combat settings has suggested that early and aggressive coagulation

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factor replacement results in lower mortality.[5] However, it is unclear whether this can be extrapolated to civilian settings where penetrating injuries are uncommon and a coordinated approach to resuscitation is possible. A recently published RCT using plasma to platelets to red cells in a 1:1:1 ratio compared with a 1:1:2 ratio showed no significant differences in mortality.[6] There is a lack of good evidence from RCTs to support recommendations about blood component usage. Our institution uses a 2:1 RBC:FFP ratio, encourages early use of platelets and suggests appropriate goal directed therapy based on frequent monitoring of Hb, platelet count and coagulation profile, aiming to maintain parameters critical for haemostasis (Hb $>$ 80 g/L, platelet count $>50 \times 10^9$/L, INR <2.0 and fibrinogen >1.0 g/L). A likely benefit of having a massive transfusion guideline stems from the adoption of a proactive rather than reactive approach to managing critical bleeding through alerting relevant staff to the situation. It also prompts frequent monitoring of haematological and biochemical parameters and enhances communication between the different teams managing the patient.

Tranexamic acid was recently shown in the CRASH-2 trial, an international, multicentre RCT, to reduce mortality in bleeding trauma patients.[7] In contrast, an RCT using recombinant VIIa failed to show mortality benefit in blunt or penetrating trauma.[8] Several reports of increased thrombotic risk serve as a warning for clinicians considering 'off-label' use of this drug.[9,10]

Outcomes of a Canadian Consensus Conference in 2011 have been published and review the available literature pertaining to several important questions regarding blood product use in trauma patients.[11] It is important to note that there is little evidence to adopt the use of such guidelines in the elective surgical patient who is bleeding.

Coagulopathy

Abnormal coagulation parameters (INR and aPTT) can often be found in ICU patients and can sometimes be associated with significant bleeding complications. It is important to clarify the aetiology of the test abnormality as this will significantly impact the management of the patient. It is also crucial to establish whether the patient is bleeding or not. Attempts to correct mildly abnormal coagulation test results in the absence of bleeding are unlikely to be successful and are of no proven benefit to the patient.

Causes

Coagulation profile abnormalities could be classified into two broad groups:

1. Factor deficiency: this is the most common form and may be due to reduced production (as seen in vitamin K deficiency, malnutrition, liver impairment, warfarin therapy and in rare cases of specific factor deficiencies) or increased consumption (as seen in sepsis, DIC, massive blood loss, ECMO). In many critical care patients a combination of these factors is present.

2. Factor inhibitors: this includes heparin, antiphospholipid antibodies/lupus anticoagulant (which unlike all the other causes listed reflect a prothrombotic tendency) and rarely specific factor inhibitors.

Investigations

Drug history, evidence of sepsis, prolonged critical illness and history of bleeding or thrombotic episodes are all relevant, as well as the results of recent and previous testing.

As heparin is a widely used anticoagulant and a frequent cause of prolonged aPTT, most laboratories will routinely perform a heparin correction test (e.g. polybrene or reptilase time). If heparin contamination has been excluded, a mixing study (repeat testing on a sample made up of 1:1 mix of patient plasma and normal plasma) will help clarify whether the abnormal test is due to a factor deficiency (corrected by the addition of normal plasma) or a factor inhibitor (persistent abnormality despite the addition of normal plasma).

Further investigations should be performed in consultation with a haematologist and may involve measuring individual factor levels and lupus anticoagulant testing.

Routine coagulation tests (INR and aPTT) are a measure only of the procoagulant factors in the coagulation cascade. They do not reflect the natural anticoagulants such as protein C, S and antithrombin nor do they reflect the fibrinolytic pathway, which are also frequently disturbed in coagulopathy due to factor deficiencies. They therefore provide only a crude estimate of the patient's bleeding risk which needs to be interpreted in light of the clinical picture.

Management

The management of coagulopathy is dependent on the aetiology as well as the clinical setting. In the absence of bleeding complications, the coagulopathy should be investigated so that treatment can be tailored to the underlying cause. It is beyond the scope of this article to discuss each situation separately, however we will mention two common problems.

Disseminated intravascular coagulation (DIC) is a complex process involving an interaction between the inflammatory and coagulation pathways resulting in increased thrombin generation and consumption of endogenous coagulation and anticoagulant factors. It simultaneously increases both thrombotic and bleeding risk, making management particularly challenging.

The management of DIC should focus on treating the underlying cause. In the bleeding patient or in situations of high bleeding risk (e.g. peri-operative), plasma and platelet transfusions may be required. Although prothrombin complex concentrates considerably minimize the volume of transfusion, they are contraindicated in this setting as they may exacerbate thrombotic risk because they lack antithrombotic factors (such as antithrombin and protein C) and may contain traces of activated coagulation factors. They should only be used if transfusion of plasma is not possible, keeping in mind that they only contain selected clotting factors.[12]

In patients with DIC who are not bleeding and do not have a high risk of bleeding, there is no good evidence to support the use of prophylactic plasma transfusion. Addressing treatment of the cause for DIC will also correct the coagulopathy.

Chronic liver disease: although patients with advanced stage liver disease have an increased risk of bleeding, particularly gastrointestinal bleeding, clotting test abnormalities in these patients correlate poorly with bleeding risk.[13] This suggests that bleeding complications arise more as a consequence of factors