Editorial

Blood – the most important humour?*

**The ancient medical concept of humourism (Hippocrates), states that four bodily fluids affect human personality traits and behaviours. Blood, or 'sanguine', according to Galen, means pleasure-seeking and sociable.*

In June 2014, the National Blood Transfusion Committee launched Patient Blood Management, supported by NHS England and the Department of Health (see http://www.transfusionguidelines.org.uk/uk-transfusion-committees/national-blood-transfusion-committee/patient-blood-management), by writing to the Chief Executive of every UK hospital and NHS Trust. The stated aims of this initiative, aimed at national and regional leaders, hospital managers and health professonals, are patient benefit by reducing inappropriate transfusions. It is an evidence-based, multidisciplinary approach to blood product utilisation and incorporates optimisation of erythropoiesis, and employment of restrictive transfusion thresholds, together with methods to minimise blood loss and allogeneic transfusion. It is therefore fitting, in this era of increased focus on blood at a high level, that *Anaesthesia* has decided to publish this special supplement *Transfusion, Thrombosis and Management of Bleeding*, a collaboration between anaesthetists, haematologists, surgeons and others, that pulls together state-of-the-art research and recommendations into a comprehensive guide to all things blood-related.

Over the last decade, there has been a massive expansion of interest in blood conservation, testing of coagulation profiles, and the use of haemostatic agents. Many have challenged the elective transfusion of red cells and other blood products, and one of this supplement's major themes is the effort to reduce transfusion via more rapid testing-based protocols [1] and substitution with pooled factor concentrates [2]. Advances have been also been made in preservation techniques for red cells, reducing the potentially deleterious effects of blood storage [3].

However, blood usage still remains high, especially in trauma, obstetrics and cardiac surgery, and there is increasing evidence that red cell transfusions themselves may be harmful, and not simply surrogate markers of illness. Red cells are administered in order to improve the oxygen carrying capacity of blood, yet doing so by increasing the haemoglobin level does not necessarily increase tissue oxygen delivery or uptake. Randomised trials have, so far, consistently supported the restrictive use of red cells, with no evidence of benefit for maintaining higher haemoglobin thresholds (a so-called liberal strategy), but the results of further large, randomised controlled trials are awaited (ISRCTN 70923932, see http://www.controlled-trials.com/isrctn).

Although most clinical practice guidelines recommend restrictive use of red cells, and many blood transfusion services have seen marked falls in overall usage, the use of haemostatic blood components such as fresh frozen plasma, platelets and cryoprecipitate has risen. In addition, individualised patient blood management has led to increased demand for specific blood concentrates and clotting factors.

A recurring theme in this supplement is the increasing use of 'point-of-care' testing, which appears to be either replacing or supplementing laboratory testing, depending on your point of view [4]. Point-of-care (or 'near-patient') testing includes thromboelastography (TEG®, Haemonetics, Braintree, MA, USA) and thromboelastometry (ROTEM®, TEM International, Munich, Germany) and is increasingly employed in both elective and emergency cases, despite concerns about accuracy and reproducibility [5]. This supplement also closely follows the publication of the latest National

Institute for Health and Care Excellence Diagnostics Guidance, addressing visco-elastometric point-of-care testing [6]. There is increasing evidence that point-of-care testing results in reduced use of blood and blood products, and this is covered in detail in a number of reviews in this supplement.

Another major, recurring theme is the replacement of fresh frozen plasma by prothrombin complex concentrate, and cryoprecipitate by fibrinogen concentrate. The use of factor concentrates is widely practised in mainland Europe, but there is inadequate literature showing their use is associated with patient benefit. There is still no data looking at the safety of using of factor concentrates in a bleeding patient, and little data on risks such as venous thrombo-embolism;it is also often forgotten that these are produced using patient-donated products and are neither artificial nor recombinant. However, despite a lack of high-quality evidence, some clinicians now use them routinely, especially in cardiac and trauma surgery, and the controversies associated with such practice are explored in detail in this supplement [7].

Other areas of practice are also controversial [8]. In trauma, the mainland European way is to 'stay and play', with early administration of tranexamic acid and utilisation of visco-elastic testing [9], whereas the North American approach is to 'scoop and run', and administer red cells:fresh frozen plasma:platelets in a 1:1:1 ratio [10]. The optimal approach remains unclear. Advances in the management of obstetric bleeding, notably postpartum haemorrhage, include increased interest in the implications of relative hypofibrinogenaemia, point-of-care monitoring and the potential to provide goal-directed therapy [11]. There is still a lack of knowledge about haemostatic impairment in parturients, and whether this differs from trauma-induced bleeding. There is ongoing debate regarding the relatively large proportion of critically ill patients who have some form of coagulopathy, with attention focusing on the identification of coagulation problems, prophylaxis against vascular thrombo-embolic events and heparin-induced thrombocytopenia [12]. All these issues are discussed within the pages of this supplement.

Intra-operative cell salvage, previously only found in the cardiac operating theatre, is now routinely used in obstetrics, major cancer surgery and large joint arthroplasty surgery. Other advances in therapeutic options include the widespread use of tranexamic acid in preventing excessive surgical bleeding [13], although not in high dose due to concerns about convulsions [14]. Trials of tranexamic acid in fields as diverse as obstetric haemorrhage, neurosurgical trauma and gastrointestinal bleeding are in progress. There are also several topical haemostatic agents on the market and, although they show potential, safety and efficacy profiles have yet to be established and large scale randomised trials performed [15].

Finally, the management of patients with inherited bleeding disorders [16], pre-operative anaemia [17], or those on anti-thrombotic therapy, particularly dual antiplatelet therapy [18], has been the subject of great discussion over the last few years.

Humourism's legacy persists in terms such as 'humoural immunity', but the ancient concept of the four humours has been replaced by more modern explanations of how the body works. As the reviews in this supplement demonstrate, we have come a long way – but still have some distance to travel.

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Review Article

Modern banking, collection, compatibility testing and storage of blood and blood components

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Summary

The clinical practice of blood transfusion has changed considerably over the last few decades. The potential risk of transfusion transmissible diseases has directed efforts towards the production of safe and high quality blood. All transfusion services now operate in an environment of ever-increasing regulatory controls encompassing all aspects of blood collection, processing and storage. Stringent donor selection, identification of pathogens that can be transmitted through blood, and development of technologies that can enhance the quality of blood, have all led to a substantial reduction in potential risks and complications associated with blood transfusion. In this article, we will discuss the current standards required for the manufacture of blood, starting from blood collection, through processing and on to storage.

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Introduction

Over the past few decades, transfusion medicine has transformed from a laboratory-based discipline to a more clinically oriented specialty, at the heart of which lies the appropriate and safe transfusion of blood to patients. Although blood transfusion is intended to be life-saving, blood itself can also potentially cause adverse reactions; hence safety measures are put in place at all stages of its collection, processing, storage and administration to patients. Increasing regulatory controls, similar to those in the manufacturing of medicinal products, ensure that blood components are manufactured according to a standardised procedure. However, unlike medicines that can be manufactured to a specified dose that is always consistent, with blood components there is variation in the dose due to donor to donor variation. In this review, we will give an overview into the mechanisms of blood collection, processing and storage, and briefly discuss the recent technologies developed to improve its safety.

Blood transfusion and the regulatory framework

Transfusion medicine must be practised within a stringent regulatory framework. The European Union (EU) blood directives set standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and components. In the UK, these directives have been transposed into law as the Blood Safety and Quality Regulations (BSQR) 2005. These regulations cover both the national blood services (called 'blood establishments' in the BSQR) and hospital transfusion laboratories [1]. In addition, guidelines on best practice, that may exceed the requirements of the EU directive and BSQR, are

published by the Council of Europe and UK Blood Transfusion services [2, 3].

Donor selection and microbiological testing

The World Health Organization promotes the principle of voluntary unpaid blood donation, and such donors have been shown to have the lowest risk of transfusion-transmitted infection. The epidemiology of infection in the population of a particular country can help guide the testing required to maximise safety of the blood supply. Careful donor selection criteria, with the use of detailed questionnaires, are aimed to exclude individuals at high risk of carrying infection or other factors that may be harmful to recipients, or risk factors that may be detrimental to the health of the donor. The risk of transmission of infectious agents is further reduced by the use of microbiological testing. In the UK, all donors are unpaid; they can donate from the age of 17 years, with the upper age limit being 65 years for first-time donors, while for regular donors there is no upper age limit. Continued donation for regular donors after 65 years is based on a satisfactory annual health review [4]. A full donor medical history will help identify those not suitable for donation (e.g. cancer, cardiovascular or renal disease). A full travel history is essential, together with any activities known to be associated with increased risk of acquiring infections with temporary or permanent deferral as needed, for example, deferral for 12 months after tattooing, whereas intravenous drug abusers are asked to never give blood [3].

Mandatory testing in the UK

Infections that pose a particular risk in relation to transmission by blood transfusion generally have a long incubation period, often causing subclinical infections, with asymptomatic individuals being long-term carriers. In the UK, all donations are tested for syphilis, hepatitis B, hepatitis C, HTLV1 and HIV. The increasing use of technology for nucleic acid testing has greatly increased the likelihood of detection. Despite these steps, infection may still be transmitted rarely due to the donor being in the incubation or 'window-period' before testing becomes positive for infective markers, or due to transmission of infections of unknown aetiology or where no screening test is available to date. Table 1 summarises testing in the UK and estimated risks for infection.

Bacterial contamination

Bacteria from the donor arm can contaminate the donated blood. Platelet components are at particular risk due to their storage at 20–24 °C, with the risk increasing with the duration of storage. It is estimated that up to one in 2000 platelet packs contain detectable bacteria five days after donation, and in the past, fatal reactions have been reported in 1 in 25 000–80 000 transfusions in the UK [5]. Steps to reduce this risk include enhanced methods of donor arm cleansing, and diversion of the first 20 ml of the donation to reduce the risk from skin contaminants. Routine bacterial screening of platelet preparations is now also in place in England and Wales, with extension of the shelf-life of the component from 5 to 7 days. The potential use of additional strategies such as pathogen inactivation (PI) that could further reduce this risk is discussed below.

Blood donation

The donor's haemoglobin level is assessed before each donation, generally by a semi-quantitative, gravimetric method, using a drop of capillary blood in a copper sulphate solution, but this may be supplemented by use of portable haemoglobinometers [7]. The EU blood directive states a haemoglobin standard of 135 $g.l^{-1}$ for a male subject donor and 125 $g.l^{-1}$ for a female subject donor [1].

Table 1 Estimated risk of transfusion-transmitted infection in the UK. Data from [5, 6].

Test	Testing introduced	Testing methods used	Approximate risk of infection
Hepatitis B	1970 onwards	Surface antigen (HBsAg)	1 in 1.3 million
HIV	1985/2002 onwards	Antibody/nucleic acid testing	1 in 6.7 million
Hepatitis C	1991/1999 onwards	Antibody/nucleic acid testing	1 in 28 million

No more than 15% of the estimated blood volume should be taken during any one donation, and in general, 450 ml ± 10% of blood is collected with an interval of 12–16 weeks between donations. Individual components such as platelets and plasma can also be collected by apheresis using a cell separator with a maximum of 24 procedures in 12 months [3].

Additional donor testing

In addition to testing for infective markers as described above, ABO and RhD grouping are determined routinely on each occasion. Typing for other Rh antigens (C, E, c and e) and K, as well as testing for haemoglobin S, are now routinely performed on all blood donations. Phenotyping for other red cell antigens such as Duffy, Kidd, and MNSs is performed on a restricted number of units to provide antigen-negative blood for allo-immunised patients. All donations are also screened for the presence of atypical red cell alloantibodies, and donations with potent clinically significant alloantibodies are not issued to hospitals. The incidence of clinically significant red cell alloantibodies in blood donors is very low (0.3%) compared with the incidence in potential recipients (1–2%). There are additional requirements for blood provision for special groups, e.g. for neonatal and intra-uterine blood transfusion, haemato-oncology and haemoglobinopathy patients [3]. Molecular techniques are increasingly available for blood group testing and extended red cell antigen genotypying, and are likely to come into more routine use within blood services with application of rapid automated technology.

Processing of whole blood into blood components

Blood components, namely packed red cells, fresh frozen plasma (FFP), cryoprecipitate and platelets, can be obtained from whole blood or by apheresis. Transfusion of whole blood is not used in clinical practice due to its limitations concerning, among other things, a it is short shelf-life and the maintenance of quality and safety.

During blood donation, approximately 450 ml of whole blood from each donor is collected directly into bags containing CPD (citrate, phosphate and dextrose) anticoagulant, to prevent the blood from clotting. Citrate binds to calcium, and therefore it prevents the activation of clotting factors and thus clot formation; citrate is the most commonly used anticoagulant in apheresis for blood component collection. Following the donation process, blood is transported under strict temperature controls within 24 h of its collection to the manufacturing sites, to initiate its processing into different components.

The separation of whole blood into its constituent components relies on the differential physical properties of blood cells (i.e. density and size), which under centrifugation separates whole blood into three layers: the bottom layer, comprised of red cells; the middle layer or 'buffy coat' (containing white cells and platelets); and the top layer, made up of plasma. The resulting product following centrifugation is then put into a pressing device, where plasma is transferred into another bag under a closed and sterile system, while red cells remain in the same bag. To preserve the viability and functionality of red cells, SAGAM (saline, adenine, glucose and mannitol) solution is added. Packed red cells should be stored at 4 °C and be used within 35 days. (Table 2) [3].

Packed red cells may also be washed using sterile saline, with the aim of removing plasma proteins and cytokines. Washed red cells are indicated for patients with severe recurring allergic reactions, for whom medication such as antihistamines are ineffective (e.g. patients with IgA deficiency who have anti-A antibodies). The washing process removes ~20% of red cells and can result in electrolyte leakage from the remaining red cells; thus, the shelf-life of washed red cells is only 24 h [3].

Platelets

Platelets can be obtained either from centrifugation of whole blood or from apheresis. In the former case, a pooling of four donations of 'buffy coat' layers is required to meet the specification of a single adult therapeutic dose (Table 2). Platelets are stored at 20–24 °C for five days under constant agitation. The storage of platelets at room temperature, however, increases the risk of bacterial growth and contamination, and thus bacterial screening tests have been introduced in some countries to reduce this risk. In addition, bacteriological testing allows for the shelf-life

Table 2 Characteristics of blood components. Values are mean (SD). Data from NHS Blood and transplant 2014, and [3, 31].

	Red cells	Pooled platelets	Apheresis platelets	FFP	MB-FFP	SD-FFP (Octaplas)	Cryoprecipitate pool
Volume; ml	220–340	295.3 (24.5)	179.5 (14.9)	275 (14)	229.5 (12.7)	200 (standardised)	204.9 (21.4)
Storage temperature	4 ± 2 °C	22 ± 2 °C with agitation	20–24 °C with agitation	< −25 °C	< −25 °C	< −18 °C	< −25 °C
Anticoagulant	CPD	CPD	Acid citrate dextrose	CPD	CPD	Sodium citrate	CPD
shelf-life	Up to 35 days	5 days (or 7 if bacterial screening)	5 days (or 7 if bacterial screening)	36 months (24 h after thawing if stored at 4 ± 2 °C)	36 months (24 h after thawing if stored at 4 ± 2 °C)	4 years	36 months (4 h after thawing if stored at ambient)
Specification	Hb > 40 g.unit^{-1}*	Platelet count ≥ 240 × 10^9.pool^{-1}*	Platelet count ≥ 240 × 10^9.unit^{-1}*	Factor VIII:C > 0.70 IU.ml^{-1}*	Factor VIII:C > 0.50 IU.ml^{-1}*	Factor VIII > 0.50 IU mL^{-1}	Fibrinogen > 700 mg. pool^{-1} and Factor VIII:C > 350 IU.pool^{-1}*
Typical values	Hb 0.41 (9.52)	Platelet count 300 (45)	Platelet count 261 (35)	Factor VIII:C 0.85 (0.2)	Factor VIII:C 0.65 (0.18)		Fibrinogen 1753 (398) mg.pool^{-1}; Factor VIII 435 (112) IU.pool^{-1}

FFP, fresh frozen plasma; MB, methylene blue; SD, solvent detergent; CPD, citrate, phosphate, dextrose.
*In greater than 75% of components.

of platelets to be extended to seven days. Other pathogen inactivation processes have been developed further to improve the safety of platelet transfusions and these are discussed below.

Plasma

Following separation from whole blood, plasma is frozen to less than −25 °C, and can be kept for 36 months (Table 2). After thawing, the shelf-life of FFP varies between 24 h in some countries (e.g. the UK), to five days in others (USA and Canada). In the UK, FFP for individuals who are born on or after 1 January 1996 (i.e. those individuals who have not been exposed to BSE through dietary intake) is imported from countries with a low risk of vCJD, and the imported plasma is additionally treated with methylene blue (see below).

Cryoprecipitate is prepared from thawed FFP which is centrifuged and the supernatant removed. The remaining precipitant is cryoprecipitate, which is enriched in high molecular weight proteins, factor VIII, von Willebrand factor and fibrinogen. Cryoprecipitate can be stored for 36 months at less than −25 °C [3]. Following thawing, cryoprecipitate should be transfused within four h. In the UK, cryoprecipitate is available as pools of five units (20 ml per unit), with an adult dose being two pools (i.e. a total of 10 units per dose) [3].

Leucodepletion and irradiation

In the UK and the USA, whole blood is passed through a leucodepletion filter before centrifugation, so as to remove the white cells. In other countries like Canada, Australia and others in Europe, the leucodepletion step is introduced at later stage of blood component processing. Leucodepletion reduces the transmission of white cell-associated infections, as well as transfusion reactions, HLA-alloimmunisation, infections and fever episodes [8].

In certain circumstances, cellular components like red cells and platelets can be irradiated by 25–50 Gyr to inactivate viable lymphocytes. Irradiated blood components are necessary for patients at risk of transfusion graft vs host disease, such as immunocompromised patients and patients who partly share genetic tissue type with the transfusion donor [9]. The irradiation of cellular components, however, shortens the shelf-life of blood components.

Pathogen reduction technology

The aim of pathogen reduction technology (PRT) is to inactivate pathogens such as bacteria or viruses in blood components and thus improve blood safety. The potential advantages of pathogen inactivation, in addition to reduction in risk of window-period infections of known transfusion-transmitted agents, are relaxation of some donor deferral criteria; and reduction in risk of unknown or emerging pathogens. Pathogen reduction technology of plasma has been used for several decades, with methylene blue and solvent detergent treatments being the most common. However, methods employing the use of Amotosalen and Riboflavin are now also in use (see platelets below).

In 2004, as a risk reduction measure for variant Creutzfeldt-Jacob disease (vCJD), the UK Department of Health recommended the use of FFP sourced from countries with a low prevalence of bovine spongioform encephalopathy for children born after 1 January 1996. However, due to the higher incidence of viral markers on US volunteer donors, their plasma was subjected to a methylene blue viral inactivation process [4].

During the methylene blue process, a single unit of plasma is illuminated with visible light in the presence of low doses of methylene blue [10]. This process results in the formation of free oxidative radicals that damage the nucleic acid of encapsulated viruses and bacteria, thus preventing pathogen replication [11].

An alternative to methylene blue-treated plasma (MB-FFP) is Octaplas (Octapharma AG, Vienna, Austria), which uses a solvent detergent treatment to inactivate bacteria, lipid enveloped viruses and most protozoa in FFP [12, 13]. Octaplas, unlike MB-FFP, is prepared from pools of donations sourced from countries with low vCJD risk. The pooling process leads to: standardisation of concentration of clotting factors; prevention of transmission of hepatitis A virus and parvovirus B19 infections through the dilution of the viral load in the starting plasma; and neutralising of immune antibodies [14]. Recently, Octapharma modified the manufacturing process for solvent detergent-treated FFP to incorporate a chromatographic step that selectively binds abnormal prion-related protein (PrP) to an affinity Ligand Gel (OctaplasLG, Octapharma, AG, Vienna, Austria). Using this procedure, Octapharma has demonstrated greater than or equal to 3.0 log reduction using scrapie models of abnormal prion protein [15]. OctaplasLG is licensed in Europe and has now replaced Octaplas. The differences between MB-FFP and solvent detergent-treated FFP are described in Table 2. Both treatment processes are known to alter coagulation factors; however, the clinical significance of this is uncertain at present.

Other newer pathogen reduction technologies that can be used on platelet concentrates have been developed as a means of reducing the risk of bacterial contamination of platelets and other infectious agents. Two systems are now CE-marked and in routine use in a number of European countries, but not yet the UK or USA, namely Intercept® (Cerus Corporation, Concord, CA, USA) and Mirasol® (CaridianBCT, Lakewood, CO, USA). A third, Theraflex (Macopharma, Tourcoing, France), uses only exposure to ultraviolet light, and is currently undergoing clinical studies to determine its efficacy and safety.

In the Intercept system, amotosalen binds non-specifically to the double stranded region of DNA and RNA of pathogens, and when exposed to ultraviolet light, it forms permanent cross-links to the nucleic acid strands, thus blocking DNA/RNA replication [16]. The system has been shown to inactivate enveloped viruses (HIV, HBV, HCV and west Nile virus) [17], Gram negative and Gram positive bacteria, and protozoa [18].

In the Mirasol system, addition of riboflavin (vitamin B2) to platelet concentrate together with ultraviolet light exposure selectively enhances damage to the guanine bases in the DNA of pathogens, thus preventing their replication [19]. There is no removal step at the end of the process, so residual riboflavin and its photo-products remain in the platelet concentrate during storage.

The available data on Intercept and Mirasol suggest that both systems are safe in terms of toxicity to cells, carcinogenicity and mutagenesis [20–22]. The recent Cochrane systematic review of pathogen-reduced platelets found no evidence of a difference in mortality, clinically significant or severe bleeding, transfusion reactions, or adverse events between pathogen-reduced (i.e. Intercept and Mirasol systems) and standard platelets [23]. Pathogen inactivation of platelets may have a number of operational advantages,

including the possibility of relaxing some donor deferral criteria especially in relation of travel; it can be used as an alternative to irradiation or CMV testing of components; and it may allow up to one day of extra useable shelf-life compared to current bacterial screening methods. Together, these factors simplify stock management and reduce wastage of platelets, but these benefits cannot be realised until a licensed system for pathogen inactivation of red cells is available.

Hospital laboratory transfusion practice

The safety of blood components is an issue that extends beyond the production stage. All hospital transfusion laboratories are required to comply with regulations concerning the handling, storage and traceability of blood components, as well as patient compatibility testing [1].

Within hospitals, systems must be put in place to ensure that the right blood is transfused to the right patients. Wrong blood given to the wrong patient can result in death, and the Serious Hazards of Transfusion haemovigilance scheme (SHOT) continues to highlight the ongoing risks of these errors [5, 6].

Compatibility testing

Compatibility testing involves the determination of patients' ABO/RhD grouping, antibody screening and crossmatching. All these aim to prevent a haemolytic transfusion reaction, by identifying a harmful antigen-to-antibody reaction in vitro that can cause problems in vivo when blood is transfused.

The ABO blood group is ascertained using forward and reverse grouping; in the former, commercial monoclonal anti-A and anti-B are mixed with a patient's red cells, while in the latter the patient's plasma is added to commercial A and B red cells.

Antibody screening tests a patient's plasma, using an indirect antiglobulin test (IAT) at 37 °C, for any unexpected clinically significant antibodies against the minor blood group system antigens. During the crossmatching test, the donor red cells are mixed with the recipient's serum to detect red cell destruction and thus prevent a transfusion reaction. The crossmatch can be completed in approximately 45 min.

The majority of laboratories in developed countries now use automated testing, with advanced information technology systems for the documenting and reporting of results. This minimises the risks of errors associated with manual testing, as well as allowing the hospital transfusion laboratory to provide ABO/RhD matched red cells to patients using electronic issue (or 'computer crossmatch'), without the need for manual crossmatch testing. To work, electronic issue requires that: data obtained from serological tests on separate blood sampling of donors and recipients be entered correctly into the computer; no clinically significant antibodies are detected in the recipient's serum/plasma; and there are at least two results on record of the recipient's ABO typing (one each from a current and historical sample) [24, 25]. Patients who have red cell antibodies, or have a history of ABO incompatible stem cell transplants, are not eligible for electronic issue; manual crossmatching should still be carried out in these cases.

Future advances

Worldwide blood shortage, stringent donor deferral criteria, costly diagnostic tests and the risk of transfusion-induced morbidity (e.g. infection from known and unknown pathogens, transfusion reactions etc.) have driven the development of blood substitutes like haemoglobin-based oxygen carriers [26] and perfluorocarbon emulsions for the replacement of packed red cells, as well as haemostatic agents instead of plasma. It is beyond the scope of this review to discuss all of them in detail, so we will only briefly mention the recent development in haemoglobin-based oxygen carriers; their potential advantages include availability, long-term storage, universal compatibility, and the absence of transfusion transmissible infections and/or diseases.

Haemoglobin-based oxygen carriers are derived from human or bovine red cells. Following red cell lysis, cell-free haemoglobin (Hb) undergoes purification through filtration, chromatographic procedures and chemical modifications [27, 28]. Commonly used formulations that have so far been tested in animals and humans include: intratetrameric cross-linked Hb; polymerisation of Hb tetramers and Hb tetramers conjugated to non-protein molecules (Table 3) [28].

However, despite intense research into this field, none of the products has a therapeutic licence for clin-

Table 3 Haemoglobin (Hb)-based oxygen carriers. Data from [28, 30].

Products	Technology	Company	Side effects
HemAssist	Cross-linked Hb tetramer	Baxter Healthcare Corporation, Deerfield, IL, USA	Death, stroke, hypertension, cardiac lesions, gastrointestinal symptoms
Hemopure	Polymerised Hb	Biopure Corporation, Cambridge, MA, USA	Hypertension, cardiac arrhythmia, decreased O_2 saturation, gastrointestinal symptoms and bleeding/anaemia
Hemospan	PEG conjugation	Sangart Inc, San Diego, CA, USA	Bradycardia, arrhythmias, gastrointestinal upset, hypertension
Optro (rHb1.1)	Cross-linked Hb tetramer	Somatogen, Inc., Baxter Healthcare, Newbury, Berks, UK)	Vasoconstriction, cardiac lesions, gastrointestinal lesions
Polyheme	Polymerised Hb	Northfield laboratories, Inc, Evanston, IL, USA	Pneumonia, multiple organ failure, coagulopathy, myocardial infarction.
Pyridoxylated Hb	Cross-linked and conjugated Hb	Apex Bioscience, Inc, Chapel Hill, NC, USA	Not reported
Hemolink	Polymerised Hb	Hemosol BioPharma, Inc, Mississauga, ON, Canada	Hypertension, myocardial infarction, gastrointestinal symptoms

ical use in Europe or US; this is due to significant morbidity and mortality seen with all of them during the clinical trials in animals and humans. Examples of some of the common adverse events seen include: hypertension; cardiac involvement; renal injury; neurotoxicity; haemostatic abnormalities and gastrointestinal complications [29, 30]. The mechanisms of haemoglobin-based oxygen carriers toxicity are not completely well understood, but some of the hypotheses discussed in the literature include: depletion of nitric oxide from the endothelium by the free Hb, leading to vasoconstriction; oversupply of oxygen, a known vasoconstrictor; haeme-mediated oxidative reactions, whereby the Hb outside the red blood cell environment undergoes spontaneous oxidation of the ferrous haeme iron ($HbFe^{2+}$-O_2) to ferric haeme ($HbFe^{3+}$), which is a toxic metal; and haeme-mediated inflammatory response [28]. Over the last few decades, research efforts have focused on overcoming some of the above issues; however, results have been disappointing and we are not yet closer to having a safe and efficacious haemoglobin-based oxygen carrier. An alternative approach to red cell substitutes is production of red cells in the lab from CD34+ cells derived either from peripheral blood, cord blood, or from embryonic or induced pluripotent stem cells. Small amounts of red cell reticulocytes that appear to be functional have been produced to date using these methods. The challenge will be to scale up these methods to produce sufficient cells for a transfusion, and to demonstrate efficacy and safety in clinical studies.

Competing interests

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Review Article

Practical management of major blood loss

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Summary

The pathophysiology of bleeding, regardless of cause, is complex and ill understood. For traumatic or sudden unexpected haemorrhage, the use of transfusion packs with red cells, fresh frozen plasma, cryoprecipitate and platelets being given in ratios of between 1:1 and 1:3 seems reasonable. This removes the requirement for 'wait and see tests' and should be part of an overall resuscitation and stabilisation plan that may improve outcome following sudden haemorrhage. The replacement of fresh frozen plasma and cryoprecipitate with low-volume, targeted concentrates is attractive. There is increasing evidence for the efficacy and safety of fibrinogen concentrates as a single agent. The combination of fibrinogen and prothrombin complex concentrates could be powerful and has the possibility to the management of bleeding and improve outcome in patients but, as yet, remains unproven.

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Introduction

Patients who are bleeding present to anaesthetists in a number of common scenarios:

1 Traumatised and in hypovolaemic shock
2 Resuscitated following trauma
3 During emergency surgery
4 During elective surgery

It is easy to understand how a severely traumatised patient who is cold, hypotensive, acidotic and coagulopathic requires a massive transfusion as part of their resuscitation. More challenging is the concept of microvascular bleeding that occasionally occurs in patients undergoing extensive elective operations. These patients are, for the most part, warm, normotensive, and with a normal acid–base balance. These two dissimilar conditions have a final common pathway [1]. This review will look at the options clinicians have when treating bleeding patients, with the aim of minimising transfusion therapy and stopping bleeding.

Defining major blood loss

In traumatised patients, major blood loss is defined as loss of 100% of the circulating volume within 24 h, at least 50% within 3 h, or bleeding > 150 ml.min^{-1} or > 1.5 ml.kg^{-1}.min^{-1} [2]. In elective surgery, definitions are not so clear. They range from rates of bleeding of greater than 4–5 ml.kg^{-1}.h^{-1} to the requirement of > 6 units of red cells and a clinical description of bleeding preventing wound closure.

There is little evidence on which to base the management of acute blood loss [3]. The successful management of the bleeding patient should use protocol-driven care requiring a team approach involving theatre staff, surgeons, anaesthetists and clear lines of communication to laboratory staff [4, 5]. Conventional transfusion therapy in the bleeding patient includes a mixture of red cells, fresh frozen plasma (FFP) and platelets.

Red cell transfusion triggers

The decision to transfuse red cells is based on the physiological improvements in oxygen delivery and

blood rheology that a red cell transfusion offers [6]. Despite this, most guidelines use a transfusion trigger for red cells based on retrospective data in Jehovah Witness' undergoing elective joint replacement [7], stable medically resuscitated patients in an intensive care unit [8] and elderly patients after repair of fractured neck of femur [9]. The latest European Society of Anaesthesiology Task Force for the management of the bleeding patient suggests that the haemoglobin should be maintained between 70 and 90 $g.l^{-1}$ [10]. It is clear that this is based on low-quality evidence. An alternative to red cells in the bleeding patient is to use cell salvage and this should always be considered if possible. However, it should be remembered that this provides only washed red cells and that failure to add any haemostatic component therapy will only worsen the development of any coagulopathy.

Fresh frozen plasma and platelet transfusions

Previously, consensus guidelines suggested that transfusion of haemostatic blood component therapies should be based on a 'timely test of coagulation' [11]. More recent guidance has now incorporated data published since the Afghan and Iraq conflicts [12, 13]. Initial retrospective data from the military suggested that the use of blood and FFP in a ratio of 1:1 led to a reduction in mortality [14]. Civilian trauma data have not been so successful. Two issues have been raised. Firstly, 'survivor bias' whereby those patients who die early, do not survive long enough to receive FFP, forcing them into the low ratio group [15]. Secondly, while initial 24-h survival may be improved, survival to hospital discharge has not, with increased rates of mortality secondary to cardiovascular volume overload, acute lung injury and the development of multiple organ failure in patients receiving more FFP [16]. The UK transfusion guidelines for major acute haemorrhage suggest four units of FFP to every six units of red cells transfused (see http://www.transfusionguidelines.org.uk.)

The scientific evidence supporting the use of FFP in patients with ongoing microvascular bleeding is less clear [17, 18]. It is suggested that FFP in volumes of at least 15–30 $ml.kg^{-1}$ should be used to replace coagulation factors in patients with ongoing blood loss and an international normalised ratio (INR) > 1.6 [19]. While it is acceptable to undertake general surgical procedures in patients with platelet counts of greater than $50 \times 10^9.l^{-1}$, neurosurgical and cardiac surgical procedures may require platelet counts of between 50 and $100 \times 10^9.l^{-1}$. In patients taking antiplatelet therapy and requiring surgical procedure, the consensus is to maintain a platelet count of greater than $100 \times 10^9.l^{-1}$ and it would seem sensible to maintain a platelet count of greater than $100 \times 10^9.l^{-1}$ in patients who are actively bleeding.

Despite changes in transfusion practice over the last 20 years, the mortality from bleeding is still 30–40% for all major trauma. The pathophysiology of bleeding and coagulopathy is still poorly understood. The importance of endothelial dysfunction in the development of trauma-induced coagulopathy has become clearer [20], and perhaps allows us to understand how a simple drug such as tranexamic acid might have been so effective in the CRASH study [21]. It is becoming clear that fibrinogen, a coagulation protein that is at the centre of our coagulation system, along with thrombin, rapidly disappears in patients who are bleeding [22]. This has led to an increase in the use of haemostatic factor concentrates (fibrinogen and prothrombin complex concentrates) in bleeding patients. These concentrates can be quickly prepared and are administered in low volumes, avoiding haemodilution and volume overload. While being widely used in Europe, their use in the UK and USA has been limited. As with other changes in haemostatic transfusion practice, there has been considerable success reported from retrospective data.

Fibrinogen

Fibrinogen is available from three sources: FFP; cryoprecipitate; and as a factor concentrate. Approximately, 1 g of fibrinogen is present in four units of FFP. Cryoprecipitate is not widely available outside the UK and USA. Fibrinogen concentrate (1 g in 50 ml, Haemocomplettan®; CSL Behring, Marburg, Germany) is only licensed for congenital hypofibrinogenaemia in the UK, but has been widely used in Europe for over 30 years and appears to have a good safety record [23]. There have been concerns raised regarding high doses of fibrinogen concentrates because a high

concentration of fibrinogen has been associated with an increased prevalence of coronary artery disease [24].

Basic science experiments have shown that the addition or administration of fibrinogen improves clot firmness, reduces blood loss and improves survival [25, 26]. As a consequence, there has been a considerable increase in clinical research into fibrinogen. At present, there are five randomised clinical trials investigating this drug, mainly in the cardiac surgical population (see http://www.clinicalTrials.gov (NCT01283321, NCT01471730, NCT00968045, NCT01623531, NCT01124981). The fibrinogen level at which treatment is required is open to debate. Historically, it was set at 1 $g.dl^{-1}$ [11, 27]. This was based upon a small set of data in which four out of four patients showed signs of microvascular bleeding at fibrinogen levels of 0.58 $g.dl^{-1}$ [28]. Recently, studies in gynaecology, neurosurgery and cardiac surgery have shown an increased risk of bleeding in patients with fibrinogen levels between 1.5 and 2 $g.dl^{-1}$ [29–32]. Laboratory measurement of fibrinogen, classically by Clauss, is time consuming and prone to errors at the extremes of values [33]. Intravenous fluids, especially hydroxyethyl starches, have been shown to affect fibrin polymerisation adversely [34]. In the bleeding patient, point-of-care tests are increasingly used. Functional measurement of fibrin polymerisation by thromboelastometry/thromboelastography has been shown to correlate with levels of fibrinogen utilising a principle whereby the platelet component of the whole blood clotting profile is inhibited [35, 36]. The commercial FIBTEM assay (ROTEM®; TEM international GmbH, Munich, Germany) inhibits platelets via cytochalasin-D, a potent inhibitor of the platelet cytoskeleton, whereas the functional fibrinogen assay for TEG® (Haemonetics Corp, Braintree, MA, USA) blocks platelet aggregation by inhibiting glycoprotein GPIIb/IIIa with a monoclonal antibody fragment c7E3 Fab (ReoPro®, Eli Lilly & Co., Indianapolis, IN, USA). The maximum amplitude following inhibition of platelets correlates with levels of fibrinogen. It is thought that a maximum clot firmness (MCF) of 7–10 mm using ROTEM correlates with a fibrinogen level of 1.5–2 $g.dl^{-1}$, with some studies targeting treatment values of 22 mm MCF, thought to correlate with a plasma value of 3.6 $g.dl^{-1}$ [37].

From 2007, retrospective reports on the successful use of fibrinogen concentrate started to appear in the literature. Weinkove and Rangarajan used a median dose of 4 g in 30 patients, bleeding from a variety of causes, who all had a fibrinogen level below 1.5 $g.dl^{-1}$ [38]. Despite a 40% mortality, it was thought that its use was successful in stopping bleeding. Fenger-Ericksen et al. reported the use of a mean dose of 2 g fibrinogen concentrate in 40 patients. A significant increase in plasma fibrinogen levels correlated with a reduction in bleeding [26]. Cardiac surgery consumes considerable volumes of blood products owing to haemodilution and the coagulopathic effects of cardiopulmonary bypass. Two differing approaches to the use of fibrinogen have been reported. Karlsson et al. gave fibrinogen prophylactically at the start of elective coronary artery bypass surgery [39]. This significantly reduced postoperative chest drain blood loss without any adverse coronary events. Rahe-Meyer et al. have developed a tool to assess bleeding, the 'bleeding mass' and a ROTEM-guided dosing regimen [37]. Their retrospective data show an impressive reduction in transfusion requirements following major aortic surgery. This was developed into a successful single-centre, randomised controlled trial in which 61 patients were randomly assigned to either fibrinogen or placebo when bleeding after major aortic surgery involving cardiopulmonary bypass. Forty-five per cent of the patients who received fibrinogen avoided any other transfusion [40]. Following on from this, a worldwide multi-centre trial (REPLACE; see http://clinicaltrials.gov/show/NCT01475669) has just been completed and should report early in 2015.

Prothrombin complex concentrate

Prothrombin complex concentrates (PCCs) are highly purified and prepared from pooled human plasma. The PCCs available in Europe are: Beriplex® (CSL Behring, King of Prussia, PA, USA) and Octaplex® (Octapharma, Lachen, Switzerland). They contain factors II, VII, IX and X as well as coagulation inhibitors protein C and protein S. Protein C inhibits coagulation by inactivating coagulation factors Va and VIIIa, whereas protein S acts as a co-factor and enhances the activity of protein C. Many PCCs also have some antithrombin III and small amounts of heparin (0.5 IU

heparin per IU factor IX). The presence of these antithrombotic constituents is thought to balance the potential pro-thrombotic effects. As they are produced from human plasma, they undergo at least one viral reduction or elimination step, and the risk of virus transmission with any PCC is considered minimal [41, 42].

Prothrombin complex concentrates are licensed in the UK for urgent reversal of the effects of warfarin [43]. They have been shown to be effective in doses of 25–50 $IU.kg^{-1}$, normalising the INR within 30 min when it is > 2 [44]. To date, there are very limited data on the use of PCCs as a sole therapy in the management of bleeding patients, and the 2007 European guidance for the management of bleeding warned against their use [27]. The latest European guidance states: '*We recommend that patients on oral anticoagulant therapy should be given PCC and vitamin K before any other coagulation management steps for severe perioperative bleeding. We suggest that PCC (20–30 $IU.kg^{-1}$) can also be administered to patients not on oral anticoagulant therapy in the presence of an elevated bleeding tendency and prolonged clotting time. Prolonged INR/PT alone is not an indication for PCC, especially in critically ill patients*' [10].

Despite the above guidance and lack of clinical data, PCCs have found a place in the emergency department and cardiac operating theatres, in combination with fibrinogen concentrate, where they have replaced FFP in many European centres. Schöchl et al. [45] reported the success of fibrinogen and PCCs when used a first-line haemostatic therapy in trauma patients. Görlinger et al. [45], in a very large retrospective review of patients undergoing cardiac surgery, showed that FFP could be replaced by the use of fibrinogen and PCCs. The use of low volume factor concentrates led to a significant reduction in the associated use of red cells, and these findings were repeated in a randomised controlled trial [47]. Of note was the fact that not only did the use of a strict transfusion protocol and concentrates reduce the transfusion burden, but they also reduced overall costs and lowered the mortality rate in the treated group.

In conclusion, the replacement of FFP and cryoprecipitate with low volume, targeted concentrates is attractive. There is an increasing body of evidence for the efficacy and safety of fibrinogen concentrate as a single agent, and the combination of fibrinogen and PCC could be powerful and has the potential to radically change the management of bleeding but, as yet, remains unproven.

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Competing interests

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Review Article

Management of traumatic haemorrhage – the US perspective

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Summary

As compared with European practice, the American approach to resuscitation from traumatic haemorrhage de-emphasises pre-hospital interventions in favour of rapid transport to definitive care; limits initial surgical interventions under the damage control model; uses crystalloid as the initial fluid of choice; and follows an empiric 1:1:1 approach to transfusion with red cells, plasma and platelets in hemodynamically unstable and actively bleeding patients. The use of bedside visco-elastic testing to guide coagulation support is not as widespread as in Europe, while the early administration of tranexamic acid is more selective.

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Introduction

Advancing basic science knowledge and the urgent need created by global conflicts in Iraq and Afghanistan have fuelled a renaissance in resuscitation research. Not surprisingly, rapid introduction of new therapies has led to diversity of practice in trauma care, even among developed countries. While every trauma system and hospital has unique features, it is possible to observe diversity at the system level between the current European and American models. This chapter will describe the predominant approach to resuscitation from traumatic haemorrhage in the United States.

Pre-hospital care and trauma systems

Most European countries have a federated system to manage trauma, characterised by national-level policies for trauma centre designation and patient triage. In the US, this model can be found in some states but not others. Approximately, two-thirds of the fifty states designate trauma centres in accordance with the published guidelines of the American College of Surgeons [1]. A small handful of states (e.g. Maryland, Pennsylvania) have standards which go beyond the American College of Surgeons' criteria; a larger minority have no effective central system, and it is up to local hospitals to determine their level of commitment to systematic trauma care. This can range from simple provision of a 24-h emergency department with no pre-hospital engagement, all the way to multi-state recruitment of trauma patients supported by a privately owned fleet of fixed-wing and rotary air transports.

The large majority of American citizens live within 60 min of a Level 1 or 2 trauma centre [2], which has fostered a 'scoop-and-run' approach to pre-hospital care. Ambulances in the US are typically manned by emergency medical technicians, often volunteers, with variable levels of training. Flight crews and urban/suburban 'chase vehicles' may bring paramedics, specially trained nurses or – rarely – emergency medicine physicians to the scene of serious injuries, but the emphasis will be on rapid transport to the closest appropriate facility. Intravenous access is typically obtained at the scene or en-route; definitive airway management will occur in some jurisdictions but not others, under a variety of protocols. Pre-hospital transfusion is practiced in

a few advanced systems, by specially trained flight medics under specific conditions of extreme need or anticipated long transport times, and often governed by a telemedicine link to the trauma centre. Future advances in pre-hospital care such as diagnostic ultrasound, point-of-care blood testing or administration of prothrombotic or antifibrinolytic agents have been proposed in some systems, but not yet implemented.

Early resuscitation

Hemodynamically unstable patients are managed in accordance with the Advanced Trauma Life Support (ATLS) curriculum of the American College of Surgeons [3]. The patient is typically admitted to a trauma bay in the hospital Emergency Department; the US has only a handful of specialty trauma hospitals. The trauma team in a Level 1 centre is led by a general surgeon with subspecialty training in trauma, emergency general surgery and critical care. The team typically includes emergency medicine physicians, nurses and technicians. Initial airway management is commonly provided by the emergency medicine personnel, with the anaesthesiologist on-call for backup.

Advanced Trauma Life Support emphasises rapid identification and treatment of active haemorrhage. Diagnosis is through physical examination, assessment of vital signs and response to an initial fluid bolus, ultrasound assessment of the pleural cavities, mediastinum and peritoneum, and radiographic studies. Most emergency departments have rapid access to computed tomography for any patient stable enough to be transported. Equipment available in US trauma bays is similar to that in Europe, providing capability for rapid intravenous access, infusion of warmed fluids and advanced hemodynamic monitoring. Rapid point-of-care laboratory testing, especially arterial blood gas assessment and visco-elastic measurement of coagulation, is less common than in European centres but is an emerging standard of care.

The concept of damage-control surgery for unstable trauma patients evolved first in the US [4], and is still more widely applied than in European practice. This philosophy emphasises rapid surgical or angiographic control of active haemorrhage while minimising any intervention that does not further this goal. A damage-control procedure includes rapid anatomic intervention for ongoing haemorrhage, without efforts to restore bowel continuity, internally fix fractures or complete an abdominal closure. These activities are deferred until resuscitation is complete and normal homeostasis is achieved – typically 24–48 h after the initial surgery. Damage control orthopaedics, a related idea, emphasises the use of external fixation in preference to early definitive fixation for pelvic and long-bone fractures [5].

Per ATLS, fluid resuscitation in the US begins with the bolus infusion of an isotonic crystalloid solution [3]. Evidence in support of the benefits of deliberate hypotensive management of patients with ongoing haemorrhage has reduced the duration of aggressive fluid administration and the total quantity given [6], but there is still substantial diagnostic value in observing the hypotensive patient's response to an initial bolus. Increase in blood pressure following a fluid bolus should be anticipated in accordance with the Frank–Starling relationship: sustained normotension typically indicates previous blood loss without ongoing haemorrhage (e.g. from an isolated femur fracture); recurrence of hypotension suggests ongoing haemorrhage (e.g. from splenic laceration) and the need for urgent definitive therapy. Failure to respond to fluids suggests either very severe pathophysiology (e.g. terminal exsanguination) or a non-haemorrhagic cause of hypotension (e.g. tamponade, tension pneumothorax, high spinal cord injury).

The use of colloid solutions for acute resuscitation in US practice is substantially less than in Europe [7]. This is due both to expense and to concerns regarding associated adverse effects such as coagulation abnormalities or renal injury, without convincing evidence of a benefit. Fewer colloid products are approved for use in the US than in Europe. Most major trauma centres in the US will initiate resuscitation with crystalloids but switch rapidly to blood products in patients with sustained or recurrent instability.

In a rapid change of practice over the past decade, most US hospitals have now established a massive transfusion protocol to ease the logistic issues which can delay timely transfusion in unstable patients [8]. While details defer from one centre to another, the massive transfusion protocol will generally enable the rapid delivery of red cells, plasma and platelets from

the blood bank to the bedside. All such protocols include a provision for the use of un-crossmatched type-O red cells when necessary, a practice which has been found to be immunologically safe in haemorrhaging trauma patients [9]. Most blood banks now also support the rapid delivery of plasma to the bedside, through a variety of mechanisms. Some centres maintain a supply of liquid plasma, some have protocols for rapid delivery of pre-thawed type-specific plasma, and some even maintain satellite stocks of thawed type-AB (universal donor) plasma in the trauma resuscitation unit [10].

The use of blood products is one of the major discriminators between contemporary European and American trauma care. The past 15 years has seen a rapid trans-Atlantic advance in understanding the pathophysiology of traumatic coagulopathy. Formerly thought to be a simple matter of depletion and dilution of factors, abetted by a change in reaction dynamics due to hypothermia and acidosis, the coagulopathy seen after major injury is now known to involve dozens – perhaps hundreds – of molecules and mediators influencing a dynamic interaction between the endothelium, platelets, red blood cells and humoral proteins. Early release of activated protein-C (and likely many other factors) after tissue injury or ischaemia promotes fibrinolysis and a coagulopathic state, even before substantial loss of blood or administration of diluting fluids [11]. While there is general agreement on the underlying mechanisms, and on the need for early therapy targeted to promote coagulation, the clinical implications of this finding have led to two different approaches to transfusion: a European approach which emphasises titrated replacement of specific clotting factors; and an American approach which advocates empiric replacement of red cells, plasma and platelets in a ratio close to that of whole blood itself.

In 2006, the first observational data on the aggressive use of plasma in resuscitation from hemorrhagic shock was published, drawn from a series of military casualties treated at the US Combat Support Hospital in Baghdad [12]. More than 30 similar articles have since been published, retrospectively examining outcomes associated with plasma use in military and civilian trauma centres [13]. When unadjusted, the majority of such studies show increased survival associated with higher ratio of plasma to red cells administered during early resuscitation. These studies are strongly confounded by survival bias; patients with more severe injuries may die after receiving red cells but before plasma is available at the bedside. Various retrospective adjustment schemes have been applied to existing data in an effort to control for this effect. Results of these studies are more mixed, with some showing a benefit associated with early plasma and others showing no effect. The obvious need for better data led to the pragmatic randomised optimal platelet and plasma ratios study, conducted from August 2012 to December 2013 and presently undergoing analysis (www.clinicaltrials.gov, NCT01545232) [14]. A total of 680 haemorrhaging trauma patients were randomly assigned to receive red cells, plasma and platelets, at a ratio of 1:1:1 vs 2:1:1. While this study will help shed some light on early resuscitation within American practice, it will not address the broader question of whether plasma or specific clotting factors are more efficacious.

Proponents of factor-based resuscitation presume that best results will be achieved by replacing only the known and necessary factors, and only in the quantities needed. Any overshoot in replacement, or administration of unneeded components – such as with the medley of factors in plasma – is assumed to increase the risk for late inflammatory and septic consequences of transfusion. This approach presumes two necessary features: that factor-specific coagulation testing can be performed quickly and accurately; and that factor-specific products are available to administer. European practices have had longer experience than American ones with the use of visco-elastic testing in the emergency department setting, and have had more factor concentrate products available for a longer time.

American proponents of 1:1:1 or 'whole blood' resuscitation note that it is easy to remember and apply, and invoke the very complexity of clotting and inflammation as the reason why a pleiotrophic product such as plasma might be preferable to a pure factor concentrate. Plasma may well contain a synergistic balance of pro-coagulants with other factors and mediators that play a positive role in resuscitation and preservation of vascular integrity. Resuscitation with plasma has been shown to better preserve the endothe-

lial glycocalyx during hypovolaemia than resuscitation with other products [15].

Based on the results of the CRASH-2 trial [16], both European and American trauma care emphasises the early administration of tranexemic acid to patients in hemorrhagic shock. In American practice, this is not a universal recommendation, but reserved for patients with a high risk for ongoing haemorrhage; in most centres, tranexamic acid is given following individual practitioner decisions rather than by a universal protocol.

Late resuscitation

Once haemorrhage is anatomically controlled and the patient is moved from the operating room or angiography suite to the intensive care unit (ICU), the clinical focus turns to the completion of resuscitation, defined as restoration of homeostasis. American practice emphasises close observation of the patient's acid–base status to guide fluid resuscitation in this period, with return of serum lactate to the normal range taken as the gold standard [17]. Delayed clearance of lactate is associated with inadequate resuscitation, and generally indicates the need for further fluid administration. The use of pulmonary artery catheterisation to guide this process has generally given way to non-invasive cardiac output measurement supplemented by echocardiography (either transthoracic or transoesophageal).

American resuscitation practice is increasingly turning towards tight restriction on transfusions in patients who are hemodynamically stable and not actively bleeding, as transfusion in the ICU has been strongly associated with adverse outcomes [18]. American practitioners will generally tolerate low haemoglobin levels and abnormal clotting studies as long as there is no evidence of clinical deterioration and no need for further surgery.

Conclusion

The American approach is rapid transport to definitive care, initial damage control surgery, crystalloid as opposed to colloid infusion, and a 1:1:1 approach to transfusion with red cells, plasma and platelets in hemodynamically unstable and actively bleeding patients. The use of bedside visco-elastic testing to guide coagulation support not yet widespread, and early administration of tranexamic acid is only selective. While individual randomised controlled trials comparing these different approaches to trauma care are unlikely given the geographic, ethical and logistic barriers, it is possible that comparative effectiveness research based on pragmatic observation of performance at the system and national level will indicate which components of each system are most effective, allowing for the eventual international convergence on a global standard of care.

Competing interests

No external funding or competing interests declared.

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Review Article

Surgery in patients with inherited bleeding disorders

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Summary

It is estimated that up to 1% of the general population has a congenital bleeding disorder. With this level of disease burden, it is more likely than not that any practising surgeon or anaesthetist will, at one time or another, have occasion to manage one such patient. Congenital haemophilia, both A and B, von Willebrand's disease, and inherited qualitative platelet defects, constitute the bulk of these disorders, with the rest distributed between much rarer conditions. Although looking after such patients will continue to pose a challenge to anaesthetists, recent and continuing advances in haemostatic products, coupled with increasing awareness of haemostatic care, means that surgery in this challenging group of patients is safer now than ever before, and can now be undertaken with a degree of confidence not possible even two decades ago. Central to these recent successes has been the continuing evolution of specialised healthcare services; in particular, Haemophilia Comprehensive Care Centres. Of equal importance, at least in developed countries, has been the ease of access to highly purified, safe and effective haemostatic products. The key to successful surgical management of the patient with a bleeding disorder is a multidisciplinary approach involving not only surgeons, anaesthetists and haematologists, but also laboratory scientists, specialist physiotherapists and haemophilia nurses. With careful planning, most surgical and invasive procedures can be carried out safely in persons with haemophilia and other bleeding disorders.

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Introduction

There are about 25 000 registered patients with known bleeding disorders in the UK. Of these, about 9000 have a congenital deficiency of one or more coagulation factors, with the majority of the remainder having von Willebrand's disease (vWD) and/or qualitative platelet disorders [1]. There are probably many more individuals with an undiagnosed inherited bleeding disorder, but a widely accepted estimate is that at least 1% of the population have a congenital bleeding disorder although the majority, fortunately, are in mild form.

With such level of disease burden, it is highly probable that most practising anaesthetists will, in their lifetime, have occasion to look after a patient with a bleeding disorder. In most Western European countries, the vast majority of patients with a known bleeding disorder are registered with and cared for by an accredited haemophilia centre. In the UK, centres with 'comprehensive care' status, of which there are approximately 25, are generally located in tertiary care units, which are often, but not exclusively, teaching hospitals. All such registered patients would be expected to be in possession of and carry a standardised bleeding disorders card with a minimum set of information: diagnosis; baseline clotting factor level; preferred factor or haemostatic agent for treatment; and contact details of the haemophilia centre where patient is registered. It is always advisable to ask to inspect these cards (Fig. 1), and to contact the respective centre whenever questions arise regarding diagnosis or treatment.

Ideally, surgical interventions in patients with bleeding disorders should be performed as elective procedures, following careful pre-, intra- and postoperative planning. Correction of the haemostatic defect(s) by administration of specific replacement therapy is mandatory, except for mild forms of some disorders which can be managed with non-specific haemostatic agents such as desmopressin acetate 1-desamino-8-D-arginine vasopressin (DDAVP), a semi-synthetic derivative of vasopressin, with or without adjuvant antifibrinolytic therapy. In the vast majority of cases, the designated haemophilia centre will plan and execute all factor administration, both pre- and postoperatively. It is highly recommended that all, but the most minor procedures, should be carried out in a Haemophilia Comprehensive Care Centre [2], with access to full coagulation laboratory facilities, specialist physiotherapy support, and outpatient specialist haemophilia nurse support. It is also important that surgeons, anaesthetists, physiotherapists and haematologists involved in patients' care are all experienced in managing such patients [3]. With careful planning, most surgical and invasive procedures can be carried out safely in patients with haemophilia and other bleeding disorders [4].

General considerations

There are no universal peri-operative recommendations guiding the surgical management of patients with bleeding disorders, with recommendations largely regional, or country, specific. Some general rules seem sensible and should be applicable to most patients. These include: the optimal timing of surgery; peri-operative venous access and blood sample; handling and transport to the laboratory; peri-operative analgesia; and postoperative care.

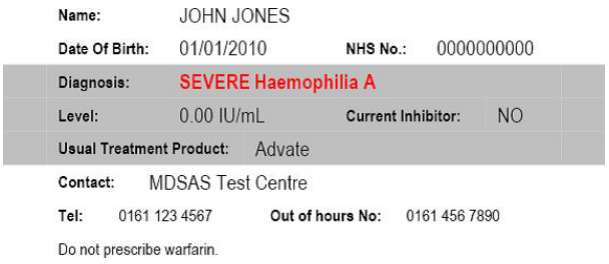
Name: JOHN JONES
Date Of Birth: 01/01/2010 NHS No.: 0000000000
Diagnosis: SEVERE Haemophilia A
Level: 0.00 IU/mL Current Inhibitor: NO
Usual Treatment Product: Advate
Contact: MDSAS Test Centre
Tel: 0161 123 4567 Out of hours No: 0161 456 7890
Do not prescribe warfarin.

Figure 1 Example of UK Haemophilia Centre Doctors' Organisation card issued to persons with bleeding disorders registered at a UK haemophilia centre.

Timing of surgery

Until full adoption of 7 days a week working practice in the NHS, elective procedures should be scheduled to take place at the beginning (Monday or Tuesday) rather than at the end of the working week [2]. In most hospitals, this ensures full availability of staff in the various departments involved in the care of the patient. It is best to avoid operations at weekends and, by similar reasoning, patients should be scheduled towards the beginning rather than the end of the working day.

Venous access

As most haemostatic agents are administered intravenously, it is crucial to establish reliable peri-operative venous access. In some situations (e.g. infants and young children), central venous access may be required and should be obtained before surgery. Blood sampling for measurement of specific clotting factors is often required to guide factor administration. To avoid a possible dilution effect, it is important to avoid sampling from veins in limbs connected to running infusions of fluid or drugs. Avoid sampling from indwelling lines, if at all possible and, unless unavoidable, arterial cannulation or punctures should be deferred until after replacement of the deficient clotting factor(s).

Handling and transport of blood samples

To avoid spurious results, blood samples for specific clotting factors and other coagulation assays should be collected in designated citrated bottles, properly filled and gently inverted several times to mix properly. Under or overfilled bottles may be rejected by the laboratory and lead to unnecessary delays in obtaining results. Blood samples should reach the laboratory, transported by hand, and be tested within 4 h (ideally within an hour) of sampling [5]. Avoid sending samples via chute systems, which may unduly agitate the blood and lead to activation of clotting factors, with ensuing spurious results.

Antifibrinolytic therapy

Peri-operative use of tranexamic acid or other antifibrinolytic agents will enhance haemostasis by promoting clot stability [6], and ideally should be administered intravenously (typically 1 g) shortly

before induction of anaesthesia. Alternatively, oral administration (1 g 3–4 times per day) may be commenced a day or two before surgery to ensure adequate blood levels are present at the time of operation.

Peri-operative analgesia

Because of their anti-platelet effects, aspirin and other non-steroidal anti-inflammatory drugs should generally be avoided, and particularly in patients with primary haemostatic disorders vWD, in whom they should be completely avoided. Paracetamol and opioids may be used safely. The use of cyclo-oxygenase-2 inhibitors such as celecoxib may be considered certain circumstances [7, 8], but this needs to be discussed in advance with the haemophilia team.

Postoperative care

A multidisciplinary approach is essential; this includes trained haemophilia/bleeding disorder nurse specialists who may be required to provide continuing domiciliary care, including factor administration, as well as physiotherapists with an interest in haemophilia to oversee the physical rehabilitation of joints, where necessary.

The main haemostatic agents employed in the management of patients with haemophilia undergoing surgery are as follows: specific clotting factor concentrates (recombinant or plasma-derived factor FVIII or IX); recombinant factor products are now the treatment of choice in the UK and the developed world; DDAVP and tranexamic acid. Highly purified plasma concentrates are still available and continue to be used in many parts of the world, and sometimes even in developed countries for specific clinical indications.

Surgery in patients with haemophilia

Haemophilia is one of the more common inherited clotting factor deficiencies, with an incidence in all racial groups estimated to be 1 in 5000 male births (haemophilia A) and 1 in 25 000 male births (haemophilia B). The two conditions are inherited as X-linked recessive disorders and have near identical clinical presentations, the most consistent being spontaneous bleeding into joints (haemarthrosis). The severity of clinical expression is largely dependent on the baseline factor level and is arbitrarily divided into three groups: severe (A or B) factor VIII or IX < 1%; moderate 1–5%; or mild > 5%.

Unlike most other coagulation factor deficiencies, phenotypic expression usually, but not always, correlates with severity. Severe forms can present with either spontaneous or traumatic bleeding while the milder forms result in excessive bleeding only in response to trauma or surgery, if not adequately treated.

Such patients may undergo surgical procedures for haemophilia-specific conditions such as end-stage haemophiliac arthropathy, or for any of the conditions that affect patients without haemophilia. The most common general surgical procedures reported from one haemophilia centre included hernia repair, cholecystectomy, and gastrointestinal procedures, representing 76% of all surgical procedures performed [9]. In addition to the general measures outlined above, all patients undergoing surgery should be fully discussed with the responsible haemophilia centre and assurances sought regarding the following:

- Pre-operative inhibitor screening. This should be performed within a week of surgery. Up to 25% of patients with severe haemophilia A, treated with factor VIII, develop allo-antibodies to factor VIII at some stage in their lives, with an estimated prevalence of between 4% and 27% [10]. The incidence and prevalence in haemophilia B is much lower (1.5–3%) [11]. Inhibitor development is one of the more serious complications of haemophilia as it renders the usual factor replacement ineffective. Most patients managed in recognised haemophilia centres are routinely screened for inhibitors at regular intervals, but it does no harm to ascertain this has been performed before surgery is undertaken.
- Availability of specific factor concentrates, not only intra-operatively, but also enough to last through the postoperative period until wound healing.
- Arrangements with the haemophilia centre regarding pre- and postoperative factor administration and the means by which peri-operative blood samples for relevant haemostatic assays will be transported to the laboratory. Again, most haemophilia centres in the UK will plan this well in advance.
- Laboratory support for the procedure. Laboratory staff should be well aware of the timing of the

operation and be ready to receive and test samples in a timely manner.

The exact factor level required for haemostasis and the duration of clotting factor replacement after surgery is not known [2, 3], but the following guidelines are generally accepted in the UK and other Western countries.

Severe/moderate haemophilia A or B

A calculated dose of the required factor concentrate should be administered within 10–20 min of commencing a of procedure. To avoid needless waste, arrangements should be made with the haemophilia team to mix and administer concentrates just before the patient is anaesthetised. Earlier pre-operative administration of factor concentrate may result in declining plasma levels of the factor should surgery be delayed or, worse still, cancelled.

Where pharmacokinetic data are available for a particular patient, the haemophilia team may choose not to measure pre-operative factor levels after administration of a calculated dose. However, in the absence of such information, a sample of blood is usually taken 10–15 min post infusion to ensure factor levels are as desired. It is generally not necessary to test for factor levels during surgery, but it is highly recommended that an immediate postoperative sample should be sent to ensure plasma factor levels are satisfactory. Levels deemed inadequate may prompt additional factor replacement at the discretion of the haemophilia team. A general guide to the required pre- and postoperative level of factor VIII for major operations is shown in Table 1.

Table 1 Coagulation factor target levels in patients undergoing major surgery. After a pre-operative bolus of factor concentrate, trough levels can be monitored before subsequent doses. Adapted from [46].

	Bolus dosing			
	Trough factor level; %		Interval frequency; h	
Day	Factor VIII	Factor IX	Factor VIII	Factor IX
1–3	80–100	80–100	8–12	12
4–6	60–80	60–80	8–12	12
> 7	40–60	40–60	12	24

Mild haemophilia A

Most patients with a mild phenotype respond very well to DDAVP and can be safely taken through even major surgery with timely administration of DDAVP, which can raise baseline factor VIII (but not factor IX) levels by three to fivefold, 30–90 min after administration [12, 13], and should be the haemostatic agent of choice. A minority of patients respond poorly or not at all to DDAVP and it is therefore important that a trial, demonstrating a satisfactory response, is conducted well before surgery and documented by the responsible haemophilia team. The recommended dose of DDAVP is 0.3 $\mu g.kg^{-1}$ administered either subcutaneously or by intravenous infusion (0.3 $\mu g.kg^{-1}$ in 100 ml saline or dextrose over 20–30 min). The half-life of the released factor VIII is about 8–12 h, similar to that of the normal circulating protein. Factor VIII levels should be measured in the immediate postoperative period at the discretion of the haemophilia team, depending on the particular procedure and the known half-life of factor VIII in the particular patient. DDAVP injection may be repeated after 12 h if needed, but once daily administration is usually sufficient. Tachyphylaxis may develop after three to five doses, and it is important to bear this in mind, although most often, the acute inflammatory response to surgery is sufficient to sustain therapeutic levels of factor VIII, thus making repeated administration unnecessary.

Repeated administration may lead to fluid retention and subsequent hyponatraemia, particularly in infants and young children (< 2 years) [14], and the elderly. It is advisable to check urea and electrolytes after three to four doses of consecutive daily administration.

Mild haemophilia B

In contrast to factor VIII, factor IX levels do not rise in response to DDAVP, which therefore, has no role in the management of haemophilia B. This means pre-operative administration of factor IX is needed to raise plasma concentration to the desired level for surgery. Factor IX, unlike factor VIII, is not an acute phase reactant and hence does not rise in response to surgery or inflammation. Consequently, postoperative replacement therapy is usually necessary to maintain levels for as long as is needed to achieve wound healing.

Surgery in patients with inhibitors

Surgery in patients with inhibitors is one of the more challenging aspects of management care. Until the mid-nineties, elective surgery in this category of patients was considered a contra-indication because of the excessive risk of bleeding [15]. However, over the past decade and a half, more such operations have been performed with increasing success [16–19]. Unlike non-inhibitor patients, those with inhibitors do not respond to treatment with the deficient clotting factor (VIII or IX), as this is neutralised by circulating antibody. At present, only the so called 'bypassing agents', activated recombinant factor VII (NovoSeven®, Novo Nordosk, Plainsboro, NJ, USA), or activated prothrombin complex concentrate, containing the activated vitamin K dependent clotting factors: IIa; VIIa; IXa; and Xa (FEIBA, factor eight inhibitor bypassing agent, Baxter Healthcare Corp, Thetford, Norfolk, UK), are available for surgery or treatment of bleeding episodes in such patients. These agents bypass the requirement for the intrinsic pathway-generated 'tenase' complex, i.e. activated factor IX and its cofactor, activated factor VIII, which activates factor X. The factor Xa so generated is a crucial step in haemostasis as it converts a large enough quantity of prothrombin to its active form, thrombin (factor IIa). This is the key enzyme that cleaves fibrinogen to fibrin, and also activates factor XIII to its active form, factor XIIIa, which is responsible for crosslinking fibrin into a stable clot. In patients with factor VIII or IX inhibitors, pharmacological doses of Novo Seven bypass this step by directly activating factor X on activated platelet surfaces at sites of vascular injury, while FEIBA bypasses the step by simply providing a ready source of preformed factor Xa. Although clinical experience has shown that both agents are effective, there is at present no validated way of predicting which of the two agents will be effective in a particular patient. Such knowledge is only gained empirically through trial. Hybrid regimens employing both have also been described.

Because the haemostatic response to bypassing agents is generally not as efficacious as for factors VIII or IX themselves, an increased risk of peri-operative bleeding should be expected. This mandates thorough and meticulous peri-operative planning and it is highly recommended that such surgery be performed only in, or at least, under the guidance of a comprehensive care centre [20]. The recommended doses of Novo Seven and FEIBA for surgery in patients with haemophilia inhibitors are shown in Table 2.

Surgery in patients with vWD

Von Willebrand's disease is the most common inherited bleeding disorder, with an estimated prevalence of 1% in the general population [21]. The true prevalence is likely to be higher because of the variable penetrance of the disorder and a wide variety of biological (e.g. ABO blood group status) and environmental factors that modulate phenotypic expression. von Willebrand factor (vWF) is an essential multifunction protein in primary haemostasis; mediating platelet to platelet adhesion, platelet to collagen adhesion and also serving as the carrier protein for circulating factor VIII. The disorder is classified into three groups as follows:

- Type 1: partial quantitative deficiency of normal VWF protein, with baseline VWF levels ranging between 10% and 40%. This is the commonest form of the disorder, representing about 75% of all cases of vWD.
- Type 2: qualitative defects in abnormal VWF protein resulting in: (i) decreased affinity and binding to factor VIII (type 2N); (ii) increased (type 2B) or

Table 2 Recommended dosage of activated prothrombin complex concentrate and recombinant factor VIIa for major surgery in patients with haemophilia and inhibitors. Adapted from [47].

	Pre-operative	Postoperative
Recombinant factor VIIa	Bolus 90–120 $\mu g.kg^{-1}$	90 $\mu g.kg^{-1}$ every 2 h for the first 48 h, then 90 $\mu g.kg^{-1}$ every 3, 4, then 6 h on days 3, 5, and 8, respectively, until discharge
Activated prothrombin complex concentrate	Bolus 75–100 $\mu g.kg^{-1}$	70 $IU.kg^{-1}$ every 8 h for at least 3 days with maximum daily dose of 200 $IU.kg^{-1}$. Dose may be tapered from day 4 to 50 $IU.kg^{-1}$ every 8 h

decreased (types 2A and 2M) platelet-dependent VWF functions.

- Type 3: complete or near-complete absence of VWF in plasma and platelets. This is the most severe form of the disorder and is characterised by a lifelong history of bleeding and VWF levels of < 10%. Because VWF is the carrier protein for factor VIII, severe vWD is also characterised by low levels of factor VIII, typically < 20%.

Desmopressin is the treatment of choice for Type 1 patients with baseline VWF level > 10 $IU.dl^{-1}$ [22]. A dose of 0.3 $\mu g.kg^{-1}$ produces a complete or partial response in over 90% of patients [23]. For patients who have been shown to mount a good response, DDAVP is administered by either the subcutaneous route, or, intravenously in 100 ml saline, approximately 40–60 min before surgery. Because VWF, like factor VIII, is an acute phase reactant, therapeutic levels sufficient to maintain haemostasis may be sustained for several days postoperatively, without the need for further DDAVP. This means checking levels postoperatively and acting accordingly. Where levels are maintained at normal or near normal levels, thromboprophylaxis should be considered in patients considered to be at high risk of venous thrombo-embolism.

Antifibrinolytic therapy (tranexamic acid) is an important adjunctive therapy, particularly in anatomical areas with high fibrinolytic activity (mucous membranes, serous cavities, oropharynx), and may be administered as a bolus intravenous dose (1 g) preoperatively [24, 25]. Alternatively, oral tranexamic acid, 1 g four times a day, may be started a day or two before surgery. Oral treatment may be continued for 3–7 days postoperatively as required.

Most patients with type 2 and all patients with type 3 vWD will require VWF concentrate administration for surgery (Table 3). A small proportion of Type 2A and 2M patients may respond to DDAVP, as well as some Type 2N patients; DDAVP is relatively contraindicated in Type 2B as it may precipitate severe thrombocytopenia. Type 3 patients do not respond to DDAVP and should always be treated with VWF concentrates before and after surgery. It is important to check postoperative levels to guide administration of concentrates until wound healing has been achieved. Again, antifibrinolytic therapy is a useful adjunctive therapy.

Pre-operative investigation

It is estimated that approximately $30 billion US dollars are spent in the USA on a whole number of pre-operative tests [26], although the clinical utility of these tests is extremely limited. No correlation between results of haemostatic tests and surgery-related haemorrhage has been found [27–29]. In a study of over 1000 patients at the Mayo clinic who underwent surgery without any pre-operative tests, outcome analyses showed a 0% death or major operative mortality and none required peri-operative blood transfusion [30]. Thus, in the absence of a personal or family history of bleeding, pre-operative haemostatic tests are of little or no value in predicting surgical bleeding, and should therefore be avoided.

Every now and then, unexpected peri-operative haemorrhage is encountered in patients not previously known to have a bleeding disorder and whose routine coagulation tests (prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT) and fibrinogen level) are normal. Most such situations can be avoided by taking a careful pre-operative history and enquiring about previous haemostatic challenges that resulted in unexpected excessive haemorrhage. Any such unexpected non-surgical bleeding should promptly be discussed with a haematologist evaluation and diagnosis. The differential diagnoses include: mild vWD with normal FVIII levels, and hence a normal aPTT; qualitative platelet disorders;

Table 3 Recommended target levels of von Willebrand factor (VWF) in patients with von Willebrand's disease undergoing surgery. Adapted from [47].

Major surgery	100% VWF pre-operatively and trough daily levels of 50% until wound healing (5–10 days)
Minor surgery	60% VWF level pre-operatively and trough daily levels of 30% until wound healing (2–4 days)
Dental extractions	60% VWF level pre-operatively (single dose)
Delivery and puerperium	80–100% VWF level pre-delivery and trough levels of 30% (3–4 days)

factor XIII deficiency; and falsely normal factor VIII levels in a person with mild haemophilia A.

Some mild haemophilia mutations result in falsely normal factor VIII levels as measured with the more commonly used routine one-stage assay. Mild haemophilia A patients carrying such mutations may present with normal routine coagulation tests and normal factor VIII levels, the diagnosis only becoming apparent when plasma factor VIII is assayed using a two-stage or chromogenic method [31, 32].

Rarer inherited bleeding disorders

The rare coagulation factor deficiencies vary from the more common haemophilia conditions in a number of ways. Data from large interventional clinical trials are limited by their rarity, and the bleeding phenotype does not necessarily correlate with the level of factor deficiency. Good correlation between factor level and bleeding phenotype is only seen in deficiencies of factors X, XIII and fibrinogen [33] (as in haemophilia A and B). They account for approximately 5% of the inherited coagulation disorders, with incidences ranging from 1 in 500 000 to 1 in 2–3 million [34]. It is worth noting that there may be clustering of such conditions because of their inherited nature. In these conditions, the bleeding history of the patient and their families is an extremely valuable guide in managing haemostasis in the peri-operative setting [35]. Specific therapeutic options that are used in the UK include both recombinant and plasma-derived products [1]. Unlike haemophilia A and B, these conditions affect both men and women, as they are usually inherited in an autosomal recessive manner [36].

Testing for these disorders usually involves a basic haemostatic screen, which may reveal abnormalities of either PT, aPTT, or both, except in the case of factor XIII deficiency when these tests will be normal. Specific factor assays will be required to determine the clotting factor and its level, and this would be carried out in a specialised laboratory. Table 4 shows the potential clotting factor deficiencies with the expected clotting screen results. Abnormal results do not necessarily indicate clotting factor deficiency, and should be interpreted with caution; for example, a potentially prothrombotic antiphospholipid antibody could cause an elevation of the aPTT [37].

As with all the bleeding disorders, the predicted severity of peri-operative bleeding will, at least partly, be based on the bleeding history, as well as the level of the deficient factor. With milder forms, and depending on the procedure, local or systemic measures such as antifibrinolytics may be all that is required. Further specific therapeutic options are detailed in Table 5 but it is worth reiterating that the peri-operative plan should be individually tailored to the patient for each procedure.

Hypo/dysfibrinogenaemia: the pivotal role in the haemostatic pathway makes inherited deficiency and dysfunction of fibrinogen a potentially life-threatening disorder. The incidence is approximately one to two per million, with autosomal recessive inheritance. Acquired deficiency, as occurs in consumptive coagulopathies, is relatively common, and many surgeons and physicians will have some experience in managing patients in whom the fibrinogen level is low.

Prothrombin deficiency: this is a very rare (one per two million) autosomal recessive condition. There are little data regarding its management, but bleeding manifestations in those with severe deficiency (4–10%) mirror those seen in haemophilia A and B.

Factor V deficiency: this is a rare (one per million), autosomal recessive condition manifesting with a more moderate bleeding phenotype. It is worth noting that factor V is synthesised both in hepatocytes and megakaryocytes, with platelets carrying approximately 20% of total factor V. The bleeding pattern for those severely affected (factor V levels < 10%) tends to be mucocutaneous.

Factor VII deficiency: this deficiency is slightly more common, with an incidence of 1 in 500 000, and

Table 4 Factor deficiencies with associated coagulation test results.

Assay	Potential factor deficiency
Prolonged PT, normal aPTT	VII
Prolonged aPTT, normal PT	VIII, IX, XI, XII
Prolonged PT and aPTT	Isolated common pathway abnormality (X, V, II, I) or combination of deficiencies (e.g. combined factor V and VIII deficiency)

PT, prothrombin time; aPTT, activated partial thromboplastin time.

Table 5 Haemostasis in the rare coagulation disorders with therapeutic options. Adapted from [36].

Factor deficiency	Haemostatic trough level	Approximate half-life of factor transfused	Therapeutic options
I	1–2 $g.l^{-1}$	96 h	Plasma-derived fibrinogen concentrate, cryoprecipitate
II	20–30 $IU.dl^{-1}$	72 h	PCC, FFP
V	15–20 $IU.dl^{-1}$	40–80 h	FFP, platelet transfusion
VII	15–20 $IU.dl^{-1}$	4–6 h	Recombinant factor VIIa, FFP, PCC
V+VIII	As for V and VIII		
X	15–20 $IU.dl^{-1}$	48 h	PCC
XI	15–20 $IU.dl^{-1}$	48 h	Factor XI concentrate, FFP
XIII	Few data; product literature [48] for Fibrogammin® recommends dosing at 35 $IU.kg^{-1}$ with expected levels of approximately 70 $U.dl^{-1}$; likely in excess of minimum requirements	150–160 h	Factor XIII concentrate, recombinant factor XIII

PCC, prothrombin complex concentrate; FFP, fresh frozen plasma.

an autosomal recessive pattern of inheritance. Severe deficiency may be associated with very mild or severe bleeding, but the typical pattern in those affected is of mucocutaneous haemorrhage.

Combined factor V and VIII deficiency: this rare deficiency of two factors results from dysfunctional endoplasmic reticulum transportation and is caused by abnormalities of the ERGIC 53 gene. Severe spontaneous bleeding is rare but one must remember to assess and replace both factors for adequate haemostasis.

Factor X deficiency: the incidence of this autosomal recessive disorder is approximately 1 per million, and severe deficiency can produce a severe bleeding disorder similar to haemophilia A. Patients may present in early life with intracranial haemorrhage.

Factor XI deficiency: whilst often grouped amongst the rare coagulation factor deficiencies, this condition has an incidence of approximately 1 in 100 000, with both recessive and dominant (autosomal) patterns of inheritance. The bleeding pattern can be highly variable; if haemorrhagic, bleeding typically occurs in areas of high fibrinolytic activity.

Factor XII deficiency: interestingly, factor XII deficiency is not associated with a bleeding phenotype even though it will prolong the aPTT and may cause undue concern in the peri-operative setting. Once found, one can feel assured that this will not cause peri-operative bleeding.

Factor XIII deficiency: this autosomal recessive disorder has an incidence of approximately 1 in 3 million. With its role in clot stabilisation, factor XIII will not be detected in the routine clotting assays that assess the formation of clot. The instability of formed clot can lead to a severe bleeding disorder, and should be considered in patients with delayed or unexplained bleeding. Classical presentation is with bleeding of the umbilical stump in the neonatal period.

Inherited platelet function disorders

These are a heterogeneous set of disorders affecting the qualitative aspects of platelets rather than the quantity. Anaesthetists are used to managing patients who are receiving anti-platelet therapy, and these disorders may be thought to be analogous in many ways. Patients may present with a history suggestive of a primary haemostatic defect, often with symptoms such as peri-operative bleeding, menorrhagia or easy bruising [38], although the more severe disorders can lead to intracranial haemorrhage and joint or soft tissue haemorrhage at a young age [39].

Testing for platelet function disorders can be challenging. A basic haemostatic screen and full blood count will show no abnormalities and, where there is a high index of clinical suspicion, platelet function testing should be performed. The options for this include aggregometry measured by either light transmission or electrical impedence, although it may be possible to detect abnormalities of platelet function using global assays such as thromboelastography or rotational thromboelastometry [40]. The current gold standard [41] is light transmission aggregometry, in which a platelet-rich plasma is exposed to various agonists and the resulting

agglutination/aggregation reactions recorded. Again, these tests are only available at specialist centres. Genetic testing is also available in the research setting but its value in decision-making is debatable.

The same principles for peri-operative planning should apply here. For minor procedures, local or systemic tranexamic acid is often the only intervention required for mild platelet function disorders. Should the disorder be more severe, or for major surgery, DDAVP may be used. This can be given intravenously or subcutaneously pre-procedure, as in the setting of mild haemophilia A, and can be given on subsequent days as required. Real time laboratory assessment is difficult in this setting, and regular clinical assessment is most routinely used. Rapid or near-patient testing should be interpreted with caution until more clinical trial data are available.

For the more severe platelet function disorders, platelet transfusions are often required to provide prompt haemostasis [42]. The transfusion-associated risks should be considered before embarking on this course of action, especially if multiple transfusions of platelets are anticipated. The major concern is the development of antibodies directed against either human leucocyte antigens (HLA) or human platelet antigens. This is of particular concern for these patients as it may reduce the effectiveness of future platelet transfusions [43]. We advise the administration of HLA-matched platelets for these patients wherever possible. One strategy for haemostasis management of conditions such as Glanzmann's thrombasthenia (see below), has been the use of recombinant factor VIIa which exerts at least some of its haemostatic effect through direct activation of coagulation, and which can be effective in some situations [44]. It would not, however be recommended for major surgery in severe disorders [45], as the effects are difficult to predict and assess, and there may be significant associated thrombotic risks.

Glanzmanns: arguably the most severe platelet function disorder, this autosomal recessive condition is caused by a reduction in the number/quality of the GPIIb/IIIa (fibrinogen) receptors on platelets. Fibrinogen, by binding to a normal GPIIb/IIIa receptor, acts as the ligand through which platelets aggregate, hence absence or faults within these receptors results in impaired aggregation. Patients may present in early life with excessive bruising, prolonged mucosal bleeding, and intracranial or soft tissue haemorrhage.

Bernard Soulier: patients with this autosomal recessive condition often have thrombocytopenia with large platelets, as well as reduced number/function of the GPIb/V/IX receptor on platelets, thereby reducing effectiveness of VWF binding which results in impaired platelet adhesion.. The bleeding diathesis is variable but can be severe in some circumstances.

Others: there is a wealth of non-specific platelet function disorders, the genetic origins of which are still being investigated (ongoing UK studies include the BRIDGE-Bleeding and platelet diseases study; the GAPP-Genotyping and Phenotyping of Platelets study). Platelet aggregometry studies show mild or marked reductions in the aggregation of platelets to various agonists.

Storage pool disorders: these disorders usually cause a mild to moderate bleeding phenotype. The pathophysiology here is disordered release of the granular constituents, either from alpha or delta platelet granules. Platelet aggregation testing may be normal or reduced, and further assays of the platelet nucleotides is required for the diagnosis, except in some circumstances in which the genetic mutation is known.

Conclusion

Patients with inherited bleeding disorders represent a higher risk population in the peri-operative setting. Although surgery in this group of patients will continue to be challenging, careful peri-operative planning, co-ordinated by an experienced haematology team, usually as part of a haemophilia comprehensive care team, should ensure a successful outcome in most cases. In individuals not previously known to have a bleeding disorder, a thorough preoperative personal and family bleeding history remains the most reliable way of detecting an underlying bleeding condition. Unselected pre-operative coagulation testing is of no value in predicting surgical bleeding and should be avoided.

Competing interests

No external funding and no competing interests declared.

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Review Article

The management of abnormal haemostasis in the ICU

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Summary

The aetiology and management of haemostatic abnormalities in critical care patients are considered in this narrative review. The mechanisms of normal haemostasis and derangements that occur as a result of sepsis and organ dysfunction are discussed. Finally, the management of haemostatic abnormalities as they relate to critical care practice are considered, including the management of heparin-induced thrombocytopenia.

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Introduction

In normal physiological conditions, the haemostatic pathways act to promote and maintain blood flow, but once a vessel is injured, they initiate a rapid response to minimise blood loss while simultaneously attempting to maintain blood flow through the lumen of the damaged vessel. Coagulation is a tightly regulated orchestration of clotting factors, co-factors and inhibitors that result in the controlled formation of the pivotal enzyme thrombin [1]. Thrombin initiates the formation of fibrin and stabilisation of the primary haemostatic plug. The final step in haemostasis is removal of the thrombus on completion of wound healing [1]. In this article, we will use the terms abnormal haemostasis and coagulopathy to describe conditions in which an individual's ability to form a clot and reduce bleeding are impaired. We will focus on abnormalities of the coagulation cascade, thrombocytopenia, and iatrogenic causes of deranged coagulation, including heparin-induced thrombocytopenia. The final section will review potential approaches to the management of patients with a coagulopathy specifically with regard to optimising patients before surgery and invasive procedures.

Burden of coagulopathy in the ICU

Coagulopathies are common in patients admitted to the intensive care unit (ICU), and are associated with poor patient outcomes [2, 3]. Thrombocytopenia develops in up to 40% of admissions, and an international normalised ratio (INR) ≥ 1.5 is encountered in almost two-thirds of patients [2, 4]. Patients are typically hospitalised for longer and are at increased risk of developing acute kidney injury and multi-organ failure [5]. Trauma patients have a higher incidence of acute lung injury, increased duration of mechanical ventilation, and an almost four-fold higher mortality if coagulopathic at presentation [6, 7].

Normal haemostasis

Figure 1 provides a summary of haemostasis. Primary haemostasis begins when the vessel wall is injured. The key elements are the vessel wall, platelets and von Willebrand factor (vWF). When the vessel is injured, smooth muscle cells in the wall mediate vasoconstriction. Increased shear stress increases the reactivity of platelets and vWF, which is crucial for the adherence of platelets to exposed collagen. The interaction of platelet glycoprotein VI and collagen triggers the recruitment of more platelets. Activated platelets

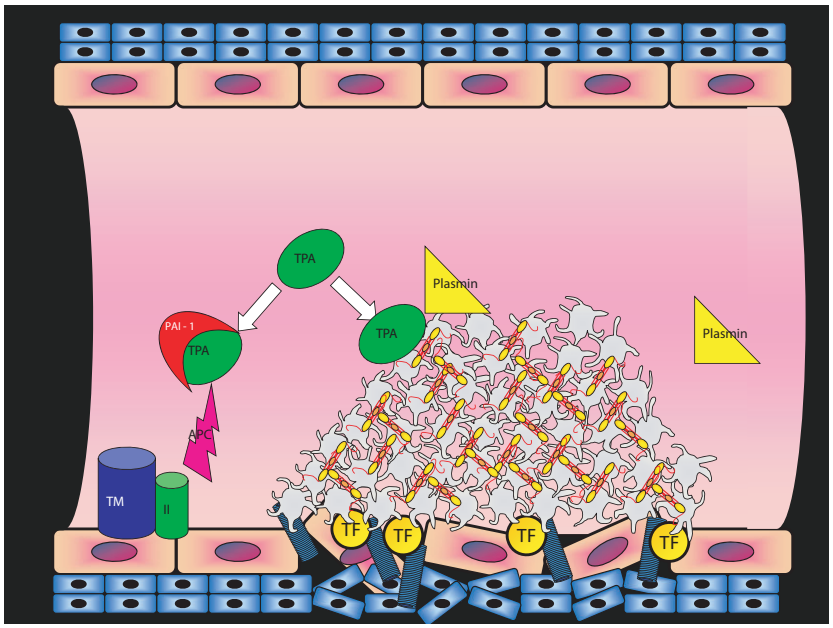

Figure 1 Vessel wall injury exposes subendothelial collagen and tissue factor. VWF binds to exposed collagen and shear forces unravel it to expose the main platelet binding site. Platelets are tethered by immobilised VWF and subsequently adhere to the exposed collagen via a variety of receptors. The binding to collagen triggers platelet activation, prompting release of activators to progressively recruit more platelets and promote formation of a platelet plug. Platelet to platelet interactions are reinforced with fibrinogen. In conjunction with platelet activation the exposure of tissue factor (TF) leads to the initiation of coagulation and the generation of thrombin, initially at the endothelial surface but ultimately on the platelet platform. The burst of thrombin generation leads to a feed forward loop recruiting more platelets, generating more thrombin and ever greater amounts of fibrinogen are converted to fibrin, which stabilises the platelet plug. All these processes are tightly localised and protected from their inhibitors by localisation on the phospholipid surface provided by platelets.

change their shape, resulting in an increased surface area and pseudopods to facilitate further binding. Platelets also release alpha granules, dense bodies and lysosomes, which provide additional coagulation factors and energy to promote the formation of the 'platelet plug'. In the microcirculation, this platelet plug is normally sufficient to stem blood loss, but it needs to be re-inforced in larger vessels that have greater blood flow and shear stress. The coagulation pathway is initiated when trace amounts of factor VII are activated by exposed tissue factor (TF). When sufficient amounts of TF are exposed, enough activated factor VII is produced to stimulate a feed-forward cascade, producing the pivotal enzyme thrombin which converts soluble fibrinogen to fibrin, stabilising the platelet plug and increasing its resistance to high shear stress. The developing thrombus is limited to the site of vessel injury by complex regulatory mechanisms that involve antithrombin, activated protein C and plasmin. The central component of fibrinolysis is plasmin, which is formed from plasminogen. Tissue plasminogen activator (t-PA) is secreted into the circulation from the endothelium and is present in a free form or bound to plasminogen activator inhibitor-1 (PAI-1). In the presence of a fibrin clot, t-PA undergoes a conformational change, upgrading its ability to convert plasminogen to plasmin. Plasmin's main substrate is fibrin but it also hydrolyses fibrinogen, factor V, factor VIII and activates the complement protein, C3. Fibrinogen and fibrin are degraded sequentially to fibrin degradation products.

Causes of acquired coagulopathy

The commonest causes are: severe sepsis; disseminated intravascular coagulation (DIC); renal impairment; liver failure; trauma; haemorrhage; and dilution of

haemostatic factors following transfusion. There are also a significant number of iatrogenic causes such as: anticoagulant medication; antiplatelet therapy; cardiac bypass surgery and intra-aortic balloon pump counter pulsation; extracorporeal membrane oxygenation; and haemofiltration. The vast majority of cases of coagulopathy in the ICU are acquired, but when present, a history of haemophilia will require specialised management from a haematologist. Table 1 lists the causes of coagulopathy in critically ill patients. The key management approach is to treat the underlying cause and not the coagulopathy solely based on the coagulation results [4]. When we consider Fig. 1, it is easy to understand why dilution of the coagulation factors or thrombocytopenia impairs thrombus formation. Coagulation is inherently based on the complex interaction and interplay of molecules. Any process, such as cooling, which potentially alters the conformation of these molecules, or a change in pH, which alters the electrostatic properties, can have a significant impact on these interactions, slowing the process and potentiating bleeding.

Table 1 Causes of acquired coagulopathy in critical care.

Secondary to disruption of homeostasis
1 Hypothermia (temp < 34 °C)
2 Severe acidosis (pH < 7.25)
3 Hypocalcaemia (ionised calcium < 1mmol.l^{-1})
Acquired platelet dysfunction
1 Liver failure
2 Renal failure
3 Acquired dysfunction secondary to extracorporeal circuits and intra-aortic balloon pumps
Thrombocytopenia
1 Haemorrhage
2 Dilution secondary to massive transfusion
3 Consumption in sepsis
4 Direct myelosuppressive effect of medication
5 Immune destruction
6 Mechanical destruction secondary to extracorporeal circuits
Deranged coagulation
1 Dilution and activation of coagulation factors
2 Vitamin K deficiency
3 Iatrogenic secondary to anticoagulants
a Vitamin K antagonists
b Heparin and low molecular weight heparin
c Novel oral anticoagulant agents, direct thrombin inhibitors and direct Xa inhibitors
4 Disseminated intravascular coagulation Hyperfibrinolysis

Pathophysiology

Severe sepsis is the commonest cause of DIC in the ICU. It is a clinical-pathological diagnosis, in which the disordered haemostasis predominantly occurs in the microvasculature [8]. An infectious organism produces the immune response, which leads to the generation of pro-inflammatory cytokines. These cytokines activate monocytes and induce expression of TF, which is the prime initiator of coagulation. The inflammatory and procoagulant responses are thus intimately entwined with cytokines, initiating coagulation and inhibiting fibrinolysis. Simultaneously, thrombin generated as part of the haemostatic process stimulates multiple inflammatory pathways leading to a deleterious cycle of progressive inflammation [9–11]. In the majority of cases, DIC presents with bleeding, although in 5–10% of cases the dominant clinical feature is organ ischaemia related to microthrombi.

The liver manufactures thrombopoietin and the majority of haemostatic proteins, both procoagulant and inhibitory [12]. The prothrombin time (PT) is a useful surrogate of liver synthetic function, as liver disease disrupts haemostasis [4, 13]. There is concomitant dysfibrinogenaemia due to the failure to remove sialic acid from fibrinogen, and increased fibrinolysis due to impaired tPA clearance from the circulation [13]. Portal hypertension also causes a reduction in circulating platelets due to splenic sequestration, and alcohol has a direct toxic effect on platelets, inhibiting their aggregation [4].

Renal impairment also attenuates haemostasis. The normal platelet response to vessel wall injury is platelet activation, recruitment, adhesion and aggregation and this is defective in advanced renal failure [14]. Uraemia causes dysfunction of vWF with decreased adhesion to platelets and also decreased release of platelet granules and their procoagulant contents [4], which impairs formation of the primary haemostatic plug. Uraemic bleeding classically presents with signs of impaired microvascular haemostasis such as purpura, epistaxis and bleeding at puncture sites. Renal replacement therapy improves platelet function in end-stage renal failure through control of uraemia [14]. In addition, anaemia caused by decreased erythropoietin synthesis in renal impairment leads to reduced axial flow of red blood cells and less marginalisation of platelets

to the vessel wall, further impairing formation of the primary haemostatic plug.

Thrombocytopenia is extremely common in the ICU, and is pivotal in the coagulopathy associated with critical illness. A UK-wide study of 29 ICUs found the prevalence of severe thrombocytopenia (platelet count $< 50 \times 10^9$ l^{-1}) was 12.4% [15]. The causes of thrombocytopenia are listed in Table 2. Over a third of those who experienced severe thrombocytopenia on the ICU died, and low platelet count independently correlated with illness severity, the presence of liver disease, and sepsis. Those patients with severe thrombocytopaenia were more likely to bleed while on the ICU, receive any form of blood product, and to die following ICU discharge. However, while thrombocytopenia appears to act as a surrogate marker of illness severity, the increased mortality in these patients was not due to haemorrhage alone.

Vitamin K deficiency is common in the critically ill, with an incidence up to 43%. Vitamin K is an essential co-factor for the synthesis of factors II, VII, IX, X, protein C and protein S. Bleeding secondary to isolated vitamin K deficiency is rare. Acquired deficiency is readily avoided by supplementing nutrition or, if enteral feeding is not possible or the patient has malabsorption, it should be given intravenously.

Clinical presentation

A critically ill patient with an established coagulopathy may not be able to provide any history, and the diagnosis may only be questioned in the light of an abnormal coagulation profile. It is imperative to appreciate that a significant coagulopathy may exist even in the presence of a 'normal' coagulation profile.

The classical clinical manifestations of impaired haemostasis are conditions that affect platelets and disorders of coagulation. Patients with platelet abnormalities or severe thrombocytopenia typically bleed immediately after trauma, whereas patients with coagulation abnormalities exhibit more delayed bleeding. Petechiae are commonly seen with disorders of platelet function and are small discrete areas of capillary haemorrhage that develop due to increased venous pressure. Classically, they are located on dependent areas of the body and in ambulatory patients the feet, ankles and legs are the commonest sites. In supine ITU patients, they tend to be more widespread. Ecchymoses are caused by the escape of blood into tissues and usually develop without a history of local trauma. They are soft tissue haematomas that develop in patients with significantly impaired coagulation.

Table 2 The investigation of thrombocytopenia in critically ill patients

Step 1: Exclude pseudothrombocytopenia
Confirm there has not been a sampling error:
- blood clot in specimen collection tube
- sample taken from arm where fluid being given
- EDTA mediated platelet clumping

Step 2: Differential diagnosis of thrombocytopenia - there are 3 distinct categories

1 Decreased platelet production
- Bone marrow failure
- Malignant infiltration
- Myelodysplasia
- Malnutrion (B12 and folate deficiency)
- Drugs
- Viral infection – HIV and hepatitis C

2 Increased platelet destruction
- Immune mediated
- Immune thrombocytopenia
- Systemic lupus erythematosis
- Antiphospholipid syndrome
- Heparin induced thrombocytopenia
- HIV
- Non-immunological causes
- Microangiopathic haemolytic anaemia (TTP, HUS, DIC)

3 Increased sequestration in the spleen
- Portal hypertension with splenomegaly
- Liver cirrhosis
- Congestive cardiac failure

Step 3: Basic investigation of thrombocytopenia
Each patient with severe thrombocytopenia (< 80 in Afro-Carribeans and < 100 Caucasians) should have the following basic investigations completed:
- Full blood count and peripheral blood film
- Measurement of vitamin B12 (preferentially halo B12)
- Measurement of folate
- Renal function tests
- Liver function tests
- INR + APTT+ fibrinogen
- HIV and Hepatitis C
- Imaging to exclude/confirm portal hypertension and splenomegaly

Investigation

In most institutions, the screening' tests to investigate abnormal haemostasis are a full blood count, PT and activated partial thromboplastin time (aPTT). The INR is the PT ratio of a test sample compared with a normal PT, corrected for the sensitivity of the thromboplastin

used in the test. The INR is sometimes reported rather than the PT. There are inherent weaknesses in these standard investigations. A normal platelet count does not exclude platelet dysfunction, such as in patients taking dual antiplatelet therapy. The PT measures the activity of the extrinsic pathway of coagulation and is dependent on the functional activity of factors II, V, VII and X. It will not detect deficiencies in other coagulation factors. The PT is also relatively insensitive and remains normal until single factor levels are below 50% of their normal value, although it is much more sensitive to multiple minor deficiencies. The aPTT measures the intrinsic and common pathways of the coagulation cascade, and is sensitive to deficiencies of factors II, V, VIII, IX, XI, XII, high molecular weight kallikrein, and fibrinogen. It is most commonly used in ICU to monitor patients receiving unfractionated heparin. As with the PT, the aPTT will be normal in a mild factor deficiency, platelet dysfunction, mild von Willebrand disease, and factor XIII deficiency. If the PT and/or the aPTT is prolonged it is important to perform a 50:50 mix of 'normal' plasma and patient plasma. If the mixture corrects the values then the patient has a factor deficiency, but if the mixture fails to correct then an inhibitor to coagulation is likely to be present. In the critically ill, this is frequently residual heparin in a patient who has undergone cardiac surgery. Failure to correct is also seen with lupus anticoagulants and acquired inhibitors of coagulations factors.

Management of coagulopathy

The key basic management principle of all coagulopathies is that the decision to transfuse blood products should not be based on the results of coagulation tests alone, rather an individualised approach is warranted. It is imperative to synthesise all the available clinical data and treat the underlying cause. When unexpected coagulation results are received in an otherwise stable patient, the key initial step is to repeat the tests. It is best to sample from a fresh site and not to aspirate blood through the lumen of a central line or arterial line, which may result in inadvertent dilution or activation of coagulant proteins. Only when two consecutive similar results have been received should more targeted investigations begin.

In practice, clinicians need to transfuse blood products when patients are actively bleeding or for prophylaxis in order to prevent bleeding. The data, particularly with regard to the prophylactic use of blood products, are very limited.

Fresh frozen plasma

The use of fresh frozen plasma (FFP) has increased in recent years, it and is now used in 11–39% of all patients admitted to the ICU [3, 16, 17]. Fresh frozen plasma is recovered from a single whole blood donation and frozen soon after collection. A typical unit has a volume of between 250 and 300 ml, and UK guidelines recommend a standard dose of 10–15 $ml.kg^{-1}$ [18]. It is defrosted immediately before use and, once thawed, contains almost normal levels of plasma proteins, including procoagulant factors and the natural inhibitors of coagulation. During active haemorrhage, it is appropriate to transfuse FFP aiming for an INR < 1.5 and an aPTT ratio < 1.5. The Intensive Care Study of Coagulopathy showed that in 50% of occasions, FFP was transfused to patients who were not bleeding and 15% of the FFP was given as preprocedure prophylaxis. Guidelines on the use of FFP recommend that it should not be used when there is no evidence of bleeding and, applying this recommendation, over a third of FFP used in current UK ICU practice is outside standard recommendations [18]. There is surprisingly little evidence demonstrating that FFP is effective at correcting mild coagulation defects, and no transfusion is completely safe [19]. In a retrospective study, patients with mild coagulopathy, the effect of 324 units of FFP were evaluated. The median decrease in the PT was 0.2 s, and normalisation of the INR occurred in only 0.8% of patients; additionally, there was no evidence of a dose–response effect [19]. In the critically ill, there is concern that the transfusion of FFP may be associated with an increased risk of transfusion-related acute lung injury.

An estimated 200 000 central venous cannulas (CVCs) are inserted annually in the UK, the majority in critically ill patients [20]. Coagulopathy is considered a relative contraindication to the insertion of a CVC [21]. Fresh frozen plasma is frequently used as prophylaxis to correct coagulopathy before CVC insertion. However, there is little evidence that FFP prevents bleeding [22], and CVC insertion is probably safe in modest derangements of the PT/aPTT [23–26]. A recently published, prospective, non-inferiority trial

specifically addressed this issue. Patients undergoing CVC insertion, percutaneous tracheostomy, chest drain insertion or drainage of an abscess, were randomly assigned to prophylactically receive 12 $ml.kg^{-1}$ of FFP, or for the procedure to be performed without intervention to specifically correct coagulopathy. The primary outcomes were the incidence of postprocedural bleeding, correction of the INR, and the occurrence of lung injury. There was no difference in the rates of bleeding or lung injury between either the groups. The INR was only reduced to less than 1.5 in 54% of the patients transfused FFP [22]. The study is limited by its small size, only 80 patients being enrolled, and patients with thrombocytopenia were not studied.

Management of thrombocytopenia

Thrombocytopenia is present in 13–50% of admissions to ICU [15, 27]. Platelet transfusions are broadly used in three clinical scenarios: firstly, when patients are bleeding as a direct result of trauma; secondly, for prophylaxis to prevent haemorrhage, particularly spontaneous intracranial haemorrhage when the count is low; and finally when patients have congenital or, more commonly, acquired platelet dysfunction. In practice, the platelet count is the trigger for most transfusions [28, 29]. Despite this, the optimal platelet count is unknown. When platelets are transfused, it is important to measure the platelet count 30 min following a transfusion to confirm that the expected rise has actually occurred. The platelet count is expected to rise by approximately $30–50 \times 10^9\ l^{-1}$ after the transfusion of a single pooled unit. Failure to increase may be due to the presence of antiplatelet antibodies, however, these are unlikely in patients who have not been transfused previously. In the critically ill, the commonest reason for the platelet count not to increase is due to the ongoing consumption of platelets, either by haemorrhage or thrombosis. The current British Society of Haematology guidelines suggest that platelet counts are maintained $\geq 75 \times 10^9\ l^{-1}$ in patients who are bleeding [30]. These recommendations were made based on expert opinion alone.

A UK study revealed that 55% of platelet transfusions occur when patients are not bleeding [15]. This is consistent with data from another group, where 66% of platelet transfusions were given for 'non-bleeding' episodes [17]. The inference is that platelets are most often given for prophylaxis, either to prevent bleeding or to cover a procedure. There are no studies that have questioned the benefit (or otherwise) of prophylactic platelet transfusions in the critically ill. One study did not find an association between thrombocytopenia and bleeding in patients who had a platelet count $< 50 \times 10^9\ l^{-1}$ for 3 days following a liver transplant [31]. Two studies have examined thrombocytopenia in patients with haematological malignancies [32, 33]. They established that platelet counts should be maintained above $10 \times 10^9\ l^{-1}$ in adult patients with leukaemia to reduce the risk of spontaneous haemorrhage [32]. One study also suggested that in patients with sepsis, a platelet threshold of $20 \times 10^9\ l^{-1}$ was required to prevent bleeding [33]. There is an urgent need to identify an optimal platelet threshold in the critically ill. It is our practice to maintain the platelet count $> 20 \times 10^9\ l^{-1}$.

Fibrinogen supplementation

Cryoprecipitate is the first-line product for the supplementation of fibrinogen. It is rich in fibrinogen, factor VIII, vWF, fibronectin and factor XIII. A standard transfusion of two bags of cryoprecipitate is expected to increase the fibrinogen concentration by between 0.5 and 1 $g.l^{-1}$ [34]. The transfusion of cryoprecipitate is appropriate when a patient is bleeding and their fibrinogen level is $< 1.5\ g.l^{-1}$. There are no randomly assigned control trials of the use of cryoprecipitate, and the recommendations are based on expert opinion. Fibrinogen concentrate is produced from pooled donor plasma, and during manufacture undergoes several steps designed to produce viral inactivation [35]. The fibrinogen is ultimately packaged as a lyophilised powder, which allows rapid reconstitution. Although appealing, there is no data to support its use over cryoprecipitate and further research is required.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a rare, adverse drug reaction caused by heparin. It is an intensely prothrombotic disorder which can be fatal when there is a delay in diagnosis. The treating team and haematology colleagues must have a high index of suspicion to facilitate diagnosis and treatment [36]. The pathophysiology of HIT centres on the development of pathological antibodies to the combination of heparin

and platelet factor 4 (PF4). These antibodies are able to activate platelets, triggering the release of their procoagulant substances and precipitating the development of pathological thrombus [37]. Heparin binding causes a conformational change in the shape of the PF4 molecule, with loss of its negative charge. This facilitates coalescence of PF4 molecules and exposes new epitopes capable of generating an immune response [38]. The activation and support of thrombin generation enables HIT to cause DIC. The probability of developing HIT is influenced by a patient's exposure to the different types of heparin. Unfractionated heparin is more immunogenic than low molecular weight heparin [39]. The antibody response is amnesiastic, and once the antibody has waned, usually after 100 days, the patient can be successfully re-challenged with heparin. If the previous coexisting stimulus is not present, and there is minimal or no PF4 release, the patient will not develop HIT.

The diagnosis is confirmed when the patient has the appropriate clinical picture and evidence of pathological heparin-dependent platelet activating antibodies. The antibodies can be demonstrated by either serotonin release assay, heparin-induced platelet activation assay, or immune assay. The degree of thrombocytopenia is usually moderate, with a platelet nadir of 60×10^9 l^{-1} in approximately 90% of cases [40]. The timing of onset of the thrombocytopenia is of key importance, with classical onset HIT occurring between 5 and 10 days after exposure to heparin. A platelet count < 20 is uncommon and should prompt re-evaluation of the diagnosis. Bleeding, particularly mucocutaneous bleeding, is unusual in HIT. Venous thrombosis (deep vein or pulmonary embolism) is common but arterial thromboses with limb ischaemia, cerebral vascular accidents and myocardial infarctions are also well described. Patients can develop necrotising skin lesions and may have a history of anaphylactoid reactions to heparin [36]. The '4Ts' score has been shown to predict the probability of HIT. The score assesses: (i) **t**iming of the onset of the thrombocytopenia; (ii) the presence or absence of **t**hrombosis; (iii) the degree of **t**hrombocytopenia; and (iv) o**t**her potential causes of thrombocytopenia.

A maximum score of 2 is awarded for each category. A low score is ≤ 3 or less, an intermediate score is 4–5 and a high score is 6–8. The scoring system is most useful if the score is low. If the score is ≤ 3, the risk of a patient having HIT is $< 1\%$. However, when the score is > 6 the positive predictive value of the test is relatively low and equates to only about a 50% chance that the patient will have HIT. Antibody testing is not warranted if the score is ≤ 3. Patients with a score ≥ 4 should have heparin discontinued and laboratory confirmation of the diagnosis expedited. They should be commenced on alternative anticoagulation with either fondaparinux or argatroban. Stopping heparin alone is insufficient and associated with a 30–50% increased risk of thrombosis at 28 days [41]. In most cases, despite stopping heparin, there will be a progressive fall in the platelet count for up to 5 days. First-line treatment is with argatroban at a dose of 0.5–1.2 $\mu g.kg^{-1}.min^{-1}$. Argatroban is an intravenous direct thrombin inhibitor with a half-life of 30–40 min. It is primarily excreted via the hepatobiliary system. It is important to note that it also causes a concomitant rise in the PT and the INR. There is considerable debate around the use of prophylactic platelet transfusion in HIT. It is important to remember that, in general, HIT is not associated with significant bleeding. It is not our practice to give platelets unless the platelet count is $> 10 \times 10^9$ l^{-1} or there is significant bleeding.

Conclusion

In summary, coagulopathy is very common in the critically ill. Blood product support is frequently required, but there is only a very limited evidence-base to support its use. Clinicians should synthesise all the data available to them at the bedside. In many cases, no specific product support is required and the key management step is the treatment of the condition underlying the coagulopathy.

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Competing interests

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Review Article

The pathogenesis of traumatic coagulopathy

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Summary

Over the last 10 years, the management of major haemorrhage in trauma patients has changed radically. This is mainly due to the recognition that many patients who are bleeding when they come in to the emergency department have an established coagulopathy before the haemodilution effects of fluid resuscitation. This has led to the use of new terminology: acute traumatic coagulopathy, acute coagulopathy of trauma shock or trauma-induced coagulopathy. The recognition of acute traumatic coagulopathy is important, because we now understand that its presence is a prognostic indicator, as it is associated with poor clinical outcome. This has driven a change in clinical management, so that the previous approach of maintaining an adequate circulating volume and oxygen carrying capacity before, as a secondary event, dealing with coagulopathy, has changed to haemostatic resuscitation as early as possible. While there is as yet no universally accepted assay or definition, many experts use prolongation of the prothrombin time to indicate that there is, indeed, a coagulopathy. Hypoxia, acidosis and hypothermia and hormonal, immunological and cytokine production, alongside consumption and blood loss, and the dilutional effects of resuscitation may occur to varying extents depending on the type of tissue damaged, the type and extent of injury, predisposing to, or amplifying, activation of coagulation, platelets, fibrinolysis. These are discussed in detail within the article.

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Introduction

Trauma remains a major cause of global morbidity and mortality, accounting for over 10% of deaths, with the majority due directly or indirectly to bleeding [1, 2]. Over the last 10 years, the management of major haemorrhage in trauma patients has changed radically. This is mainly due to the recognition that many patients who are bleeding when they come to the emergency department have an established coagulopathy before the dilutional effects of fluid resuscitation. Traumatic coagulopathy has been demonstrated in patients who received little or no intravenous fluid therapy, negating the long-held belief that iatrogenic haemodilution is the main causative factor in traumatic coagulopathy [3–6]. This has led to the use of new terminology: acute traumatic coagulopathy (ATC); acute coagulopathy of trauma shock or trauma-induced coagulopathy. In this review, we will use the term ATC. The recognition of ATC is very important because we now understand that its presence is a prognostic indicator, as it is associated with poor clinical outcome [7]. This has driven change in clinical management, so that the previous approach of maintaining an adequate circulating volume and oxygen carrying capacity before, as a secondary event, dealing with coagulopathy, has changed to haemostatic resuscitation as early as possible. However, the type of haemostatic resuscitation varies, with the USA giving

fresh frozen plasma, while there is a different approach in Europe, led by Austria, where fibrinogen concentrates are used and supported by other factor products. The divergence in clinical practice reflects our limited understanding of ATC and comparisons between approaches need to be addressed in clinical trials.

The range of bleeding injuries is wide, and one has to question whether injuries from civilian, compared with military, trauma result in similar haemostatic changes. Military casualties commonly suffer blast injury (primary blast wave, thermal and chemical burns, penetrating fragment wounds, and blunt trauma) from high-energy munitions as well as penetrating trauma from high velocity gunshot wounds. The different mechanisms of injury and increased energy transfer that occur after military trauma may or may not result in different pathophysiological responses when compared with a civilian after a road traffic accident or stab wound. Understanding the admission coagulopathy profile of a military or civilian patient will help to inform future transfusion resuscitation protocols and may help to develop potential medical therapies that will be of benefit. This article summarises the authors' current understanding of the pathogenesis of ATC.

Clinical definition

The concept of ATC stems from the recognition that a prolonged prothrombin time (aPTT) and/or activated partial thromboplastin time (PT) at hospital admission, before resuscitation, is associated with a three to four-fold higher mortality rate and is independently associated with increased transfusion requirements, organ injury, sepsis and critical care length of stay [4]. In two large observational studies, one quarter of trauma patients had prolongation of PT and/or aPTT on admission, which was independently associated with bleeding and death [7]. The development of ATC occurs as a function of the extent of tissue damage and duration of shock.

The tests used to describe ATC have varied between studies, and have included standard plasma-based tests resulting in definitions based on abnormal: aPTT; PT; thrombin time (TT); international normalised ratio (INR); platelet count; fibrinogen level; disseminated intravascular coagulation (DIC) score of 1–4 (non-overt DIC) or ≥ 5 (overt DIC) or abnormalities in clotting amplitude and clot lysis in whole blood visco-elastic tests [5]. While there is as yet no universally accepted assay or definition, many experts use prolongation of the PT to indicate that there is, indeed, a coagulopathy. Ironically, the abnormal test results that have heightened our awareness of ATC may have contributed to well-intentioned but physiologically misguided therapeutic strategies.

Phases of ATC

There are different temporal phases in the evolution of ATC. The first phase is an immediate activation of multiple haemostatic pathways, including fibrinolysis, in association with tissue injury. The second phase is due to resuscitation-related factors, for example the use of colloids and red cells will dilute haemostatic factors; and post-resuscitation, there is an acute phase response leading to a prothrombotic state, predisposing to later venous thromboembolism. In some patients, especially if resuscitated late or inadequately so that there is continuing tissue hypoxia, DIC may ensue.

Immediate effects of tissue injury

The following may occur to varying extent depending on the type of tissue damaged, the type and extent of injury, predisposing to, or amplifying, ATC:

(1) *Consumption and loss.* Coagulation factors and platelets are consumed during the formation of extravascular clots and thrombus (thrombus is a clot formed within a vessel wall), as well as external loss from the intravascular compartment during bleeding. A reduction in circulating red cells has a major effect on primary haemostasis through reduction in axial blood flow. Red cells usually flow through the centre of an artery or arteriole, and platelets and plasma are pushed to the vessel wall, so that when a vessel is severed the necessary haemostatic factors are close by; this is disrupted once the haematocrit falls below about 30% [8], such that there is an inverse correlation between the haematocrit and in vitro bleeding time [9].

(2) *Dilution*. The reversal of Starling forces and consequent shifts of interstitial fluid into the vascular

compartment results in autodilution of haemostatic factors. This is aggravated by replacement of lost whole blood with crystalloid, colloid and red cell transfusion. Even so-called balanced transfusion strategies, such as 1:1:1, that attempt to deliver the functionality of whole blood with red cells, plasma and platelets in equal ratios, deliver a dilute final product due to the presence of anticoagulants and red cell additive solutions. The final 1:1:1 product has a haematocrit of 29%, a platelet count of about $80 \times 10^9.l^{-1}$ and coagulation factors diluted to 65% of normal. Ultimately, the resultant dilutional coagulopathy is proportional to the volume of fluid administered, both in vitro and in vivo [10, 11].

(3) *Hormonal and cytokine changes* follow tissue injury. The levels of cytokines and hormones such as epinephrine and vasopressin rise, hormone and thrombin production leads to endothelial cell activation (ECA). Tissue plasminogen activator (t-PA) and Weibel–Palade body contents are released from the endothelium after stimulation by vasopressin. Weibel–Palade bodies anneal with the endothelial wall releasing von Willebrand factor and exposing P-selectin present on their inner wall, onto the surface of the endothelial cell, enhancing platelet recruitment. Cytokines, such as TNF and IL-1 as well as thrombin and continued hypoxia, cause ECA and lead to a slow change in endothelial cell phenotype from antithrombotic to prothrombotic which, in inadequately resuscitated patients, leads to DIC. Endothelial cell activation down-regulates thrombomodulin and fibrinolysis, (PAI-1 levels increase) causing cleavage of glycosaminoglycans and sloughing of the glycocalyx from the cell surface, limiting activation of antithrombin; increases in platelet activating factor production increase endothelial permeability and, in vitro, up-regulates the expression of tissue factor [12, 13].

(4) *Hypoxia, acidosis* and *hypothermia*. This triad predisposes to bleeding by impairing the function of platelets and coagulation proteases while increasing fibrinolysis [14]. Hypoxia exacerbates ECA, and coagulopathic changes are most pronounced once the pH is < 7.1 [15] and core temperature is < 33 °C [16].

(5) *Immune activation*. Tissue damage and shock are associated with platelet release of soluble CD40-ligand, a potent immune activator that itself can cause further ECA and platelet activation, and is known to be necessary in order to stabilise thrombi [29]. Immune stimulation, including complement activation, is associated with release of damage-associated molecular patterns (DAMPs), such as mitochondrial DAMPs and histone-complexed DNA [30, 31]. Immune activation can aggravate tissue damage through mechanisms including proteolytic degradation and oxidative stress, thus amplifying haemostatic activation.

Pathophysiology

Current available evidence suggests that ATC is due to massive stimulation of thrombin generation, fibrinogen and platelet consumption, and fibrinolysis by damaged tissues. Tissue damage exposes tissue factor (TF), which is present on all cells within the body that are not normally in contact with the blood, and also the sub-endothelial matrix. Tissue factor drives localised thrombin and fibrin generation. Collagen within the sub-endothelial matrix binds to platelet glycoprotein VI and vWF to glycoprotein Ib, causing platelet activation. Activated platelets adhere to damaged tissues and serve as catalysts for amplification of thrombin generation. These processes are reflected in the findings of observational clinical studies that show reduced clotting factor and physiological anticoagulant levels [21–23], high thrombin generating capacity [3, 4, 21, 24–26] and reduced platelet counts [27, 28] Overall, these data indicate a consumptive coagulopathy. The most depleted coagulation factors are fibrinogen and factor V [22, 28], which are likely consumed in part by activated Protein C or free plasmin [29, 30], although the relative importance of these proteases in reducing factor levels remains unknown.

Thrombin is the key effector molecule in haemostasis; its generation not only converts fibrinogen to fibrin but, like a cytokine, it also activates platelets, leucocytes and endothelium. Thrombin is also a major stimulator of endothelial t-PA secretion, an effect previously known as secondary fibrinolysis (as fibrinolytic activation is secondary to coagulation activation). Stimulation of t-PA release from the endothelium by

other factors such as hypoxia, epinephrine and vasopressin, is known as primary fibrinolysis. High t-PA levels have been reported in coagulopathic trauma patients [4, 26]. In addition, when bound to the endothelial receptor, thrombomodulin, thrombin activates Protein C.

It has been proposed that activated protein C (aPC) is a major effector of ATC through cleavage of factors Va and VIIIa. In addition, by binding PAI-1 and de-repressing t-PA, it may activate fibrinolysis [3, 5, 29]. This mechanism is plausible but problematic due to the kinetics of the reactions. Platelets and plasma Factor Va are resistant to aPC cleavage at concentrations of aPC seen in ATC or even therapeutic use of recombinant human aPC in sepsis [31]. As a normal platelet count of 200×10^9 l^{-1} overcame aPC anticoagulant effects even at very high concentrations of aPC, and there was no detectable effect on fibrinolysis with or without platelets [31], it is difficult to envisage how aPC could drive the phenotype described as ATC. Furthermore, though factor V is depleted and PC converted to aPC in ATC, it has been amply demonstrated that thrombin generation potential is dramatically elevated in trauma patients; this is surely inconsistent with the notion that aPC is inhibiting thrombin generation by inactivating factor V [32]. Also, it must be noted that PAI-1 is a potent inhibitor of aPC in the presence of vitronectin [33]. It is unlikely that inactivation of aPC by vitronectin/PAI-1 would lead to PAI-1 depletion and acceleration of fibrinolysis, as PAI-1 circulates at about ten times higher levels than aPC [34, 35]. It seems more likely that the enormously increased release of t-PA due to epinephrine, vasopressin and thrombin signalling drives the fibrinolytic phenotype of ATC.

The CRASH-2 trial underscored the central role of fibrinolysis in ATC by demonstrating a one-third reduction in death due to haemorrhage in trauma patients given tranexamic acid (TXA), which inhibits activation of plasminogen to plasmin [36, 37]. Other clinical studies have reported that fibrinolytic activation is correlated with transfusions [38] and mortality [38–42]. The plasmin–antiplasmin complex (PAP) is perhaps the most sensitive indicator of fibrinolytic activation, and its levels are increased in approximately 60% of trauma patients [43]. Plasmin activation and generation of fibrin degradation products such as D-dimers [3, 4, 39, 44–46] are characteristic of bleeding trauma patients. Furthermore, free plasmin can break down coagulation factors, and the extent of this effect has not been fully evaluated in traumatic coagulopathy [47].

The pathophysiology of ATC evolves after the immediate haemostatic effects triggered by tissue injury. Endothelial cell activation, stimulated by thrombin and various cytokines, as well as hypoxia and hypoperfusion [48], generates a prothrombotic environment. Hypoperfusion plays a critical role in the pathogenesis of ATC as demonstrated in numerous clinical studies [3, 6, 42–51], animal models [6, 50] and in vitro experiments [22, 51]. These data indicate that as shock severity increases, the PT and INR rise [4, 5, 7, 52] and coagulation factor levels fall [6, 48]. The most compelling of these studies, that included 3646 patients, demonstrated that ATC (INR > 1.2) occurred only when significant hypoperfusion (base deficit > 6 $mmol.l^{-1}$) was combined with severe injury (Injury severity score > 15) [6].

As ATC evolves over time, the prothrombotic effects of endothelial cell activation eventually predominate, particularly if hypoxia and acidosis are not alleviated. Many factors contribute, but release of phosphatidylserine positive microvesicles from the endothelium exacerbates the prothrombotic environment [53]. A net production of PAI-1 over t-PA further leads to shutdown of fibrinolysis [4, 25, 45]. This may explain why antifibrinolytic treatment at this stage may worsen outcome [40].

Platelets form the scaffold of clots during primary haemostasis, and serve as the catalysts of coagulation in the current cell-based model of coagulation. Platelets are relatively unresponsive to collagen, ADP and arachidonic acid after trauma [54, 55]. The pathophysiology underlying this dysfunction, which remains obscure, probably explains improved outcomes associated with platelet transfusion despite adequate platelet counts [56, 57]. Lower platelet counts on hospital admission predict trauma mortality, even when within the normal range [58, 59]. Furthermore, outcomes may be determined by the quality of transfused platelets [60].

Cellular microvesicles also contribute to normal haemostasis. Tissue factor initiates clot formation

when P-selectin glycoprotein ligand 1 (PSGL-1)/TF-bearing microvesicles from monocytes interact with P-selectin on platelets attached to injured tissue [61]. This procoagulant microvesicle production increases in trauma [62] and accelerates prothrombotic change [63].

In some ways, the initial changes of ATC are similar to DIC [40, 64]. However, in most trauma patients, there is no evidence of inappropriate disseminated clot formation on histological examination [65], so early ATC is not DIC.

The importance of rapidly identifying coagulopathy

Severely injured patients are more likely to suffer from haemorrhagic shock, require massive transfusions, and are at high risk of death due to bleeding. Acute traumatic coagulopathy is the key pathophysiological derangement, driven by tissue damage, which results in TF exposure, shock and hypoxia, and must be mitigated to successfully resuscitate the patient [66, 67].

Predicting coagulopathy

Scoring systems have been developed for adult and paediatric trauma populations that predict which patients will develop severe haemorrhage and require massive resuscitation. Algorithms based on these scores shift clinical management from a reactive to a proactive stance [66–71]. Unfortunately, none of these scoring systems identify all patients at risk of ATC and death due to bleeding. Therefore, it should be assumed that any patient considered at risk of exsanguination is at risk of ATC and death [70].

Current methods for ATC diagnosis and their pitfalls

Standard coagulation tests

These include PT-based tests (PT, INR), aPTT and Clauss fibrinogen. The PT/INR is considered an adequate screen for multiple coagulation factor deficiencies, and was thus adopted as a marker of ATC [28]. Every laboratory can provide PT, aPTT and fibrinogen results, and they are useful in guiding transfusion and predicting mortality [51].

Originally, these tests were designed to evaluate clotting factor deficiencies, not acquired multiple factor-based coagulopathies, and they are not predictors of bleeding in these circumstances [72]. Moreover, they do not take into consideration the contribution of platelets to haemostasis, the role of fibrinolysis, thrombin generation, or the interactions between coagulation enzymes and cellular phospholipid surfaces. Furthermore, these are not point-of-care assays and turnaround times often negate the value of the results [5]. Therefore, plasma-based coagulation assays are rarely helpful in the immediate management of ATC, but they do have an important role in monitoring ongoing bleeding, to guide the use of appropriate blood products.

Thromboelastography and thromboelastometry

Increasingly, TEG® (Hemonetics Corporation, Braintree, MA, USA) and ROTEM® (TEM International GmbH, Munich, Germany) are being used to guide trauma resuscitation [38, 41]. Minimally injured patients tend to have normal profiles, whereas moderately or severely injured patients typically exhibit TEG changes [38, 46]. Thromboelastograpy and ROTEM can play a role in the diagnosis of severe fibrinolysis, but are insensitive to more limited fibrinolytic activity [73]. Marked fibrinolysis detected by TEG or ROTEM is associated with a poor prognosis. Schöchl et al. [41] and others have defined hyperfibrinolysis as a reduction in maximal amplitude (MA) of 15% on ROTEM testing. However, this definition conflicts with the classic understanding of hyperfibrinolysis, which describes a kinetic reversal whereby fibrinolytic activity is greater than fibrin formation, and clot strength is compromised [74]. Thrombolastographic hyperfibrinolysis should perhaps be used to describe increased lysis only in relation to TEG visco-elastic measurements.

There is no commonly accepted visco-elastic definition of ATC, although the candidates include: increases in clotting time and clot formation time; and loss of clot amplitude (CA) and maximal clot amplitude [40, 50, 75]. One group used ROTEM to define an EXTEM CA5 (CA at 5 min) value of < 36 mm as diagnostic of ATC [5]. Another group suggests that TEG or ROTEM A10 correlates well with platelet count and fibrinogen level and predicts transfusion requirements. Advocates for visco-elastic monitoring suggest that the capacity to distinguish specific haemo-

static abnormalities provides a means of individualising coagulation and transfusion management [37, 41]. However, there are no ROTEM and TEG algorithms validated by randomised trials. Another important limitation is that, like other standard coagulation tests, TEG and ROTEM are typically performed at 37 °C, and results underestimate coagulation disturbances in hypothermic patients.

The evolving importance of ATC in trauma resuscitation

The recognition of ATC has driven dramatic change in trauma management. Until the military experience in Iraq and Afghanistan was published over the last 10 years, resuscitation was started with red cell concentrates, and scant attention was paid to coagulopathy until much later. Retrospective data from the USA and UK military and leading civilian institutions described improved outcomes in those treated with fresh whole blood [76–78] or fresh frozen plasma (FFP), cryoprecipitate and platelets in combination with red cells and tranexamic acid, with extremely limited use of colloid or crystalloid infusions [76–82], a practice known as haemostatic resuscitation [83]. It is possible that current transfusion strategies can be optimised to further improve survival after ATC [84]; the results of randomised controlled trials will guide further developments [85]. In North America, the challenge of managing ATC has generated renewed interest in whole blood for trauma resuscitation [86–89]. On the other hand, in some European countries, fibrinogen and other factor concentrates have replaced FFP in the management of ATC [90]. The evolution of divergent clinical practices underscores the need for a better understanding of the pathophysiology of ATC and for more clinical research looking at the full risks and benefits of improved haemostatic management. For example, there are no studies looking at the effect of modern treatment on the rate of post-trauma venous thromboembolism, which is a major cause of morbidity and mortality. It is recognised that the use of prothrombin complex concentrate may induce later prothrombotic changes [91], and potentially this may affect the rate of posttrauma thromboembolism.

Conclusion

Over the last decade, the incidence and implications of ATC have become clearer to the trauma community. Further clinical studies are required to increase our understanding of the pathophysiology of traumatic coagulopathy and inform the direction of studies to improve haemostatic management and outcomes.

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Review Article

Haemostatic management of obstetric haemorrhage

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Summary

The haemostatic management of major obstetric haemorrhage remains challenging, and current published guidance relies heavily on experience from the non-pregnant population and expert opinion. In recent years, an interest in the implications of relative hypofibrinogenaemia, point-of-care monitoring of coagulation abnormalities, and the potential to give goal-directed therapy to correct coagulopathies, have created the possibility of significantly challenging and changing guidance. There is evidence that the haemostatic impairment in the pregnant population is different from trauma-induced bleeding, and the type and rate of onset of coagulopathies differ depending on the underlying cause. This review examines areas such as possible intervention points, describes evidence for over-transfusion of fresh frozen plasma in some situations and challenges conventional thinking on formulaic management. It also examines the rationale for other therapeutic options, including fibrinogen concentrate and tranexamic acid.

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Introduction

Bleeding at the time of childbirth remains a common and demanding clinical emergency. It is the leading cause of maternal mortality in resource-poor countries [1, 2], and severe morbidity in resource-rich countries [3, 4]. The incidence of postpartum haemorrhage (PPH) has increased in many countries [3, 5–7], and the rate of PPH > 2500 ml in the Scottish maternal morbidity reports has remained almost unchanged at around 5.8 per 1000 (2009–12), despite changes in obstetric strategies [3]. Obstetric haemorrhage has different aetiologies; uterine atony and surgical and genital tract trauma account for 80%, but in patients with more severe bleeding, where the likelihood of coagulopathy increases, other causes such as uterine rupture, abnormalities of placentation (accretia and praevia) and abruption are increasingly represented [8].

There is limited evidence on appropriate intervention points and management strategies related to the haemostatic management of obstetric haemorrhage, with much of the literature and clinical guidelines relying on audit, interpretation of secondary outcomes, and extrapolation from major trauma [8, 9]. National Institute for Health and Care Excellence (NICE) and World Health Organization (WHO) guidelines offer no advice on haemostatic management of PPH [10, 11]. We have therefore included a section on our current practice based on a pragmatic interpretation of the literature.

Definition of obstetric haemorrhage

Definitions vary, but usually include blood loss in excess of 500 ml at the time of vaginal delivery, or 1000 ml at caesarean section, and bleeding of this amount is common (about 1 in 20 births). Major PPH is classified as moderate between 1000 and 2000 ml and severe over 2000 ml. Other definitions include a fall in haemoglobin concentration (Hb) of ≥ 40 g.l^{-1}, the need for the transfusion of ≥ 4 units of red cells, or the need for an invasive procedure [8]. Massive PPH has also been described as bleeding of > 2500 ml, and is associated with significant morbidity such as intensive care admission and emergency hysterectomy [3]. A limitation of interpreting risk factors for PPH and the effectiveness of treatments is the inconsistent use of definitions, making direct comparisons difficult.

Changes in haemostasis at term

At term, haemostasis is tipped towards a prothrombotic state, with levels of all procoagulant factors, except factor XI, increased [12–14]. This is especially marked for fibrinogen, von Willebrand factor and factor VIII [14], with levels typically increased by more than 100%. At term, the fibrinogen level is 4–6 g.l^{-1}, compared with the non-pregnant normal range of 2–4 g.l^{-1} [15, 16]. These changes result in shorter prothrombin and activated partial thromboplastin times (PT/aPTT), sometimes below the normal laboratory range, and a large increase in thrombo-elastographic parameters such as maximum clot firmness (MCF) and maximum amplitude (MA) [17–21].

Natural anticoagulants such as protein S fall, contributing to the prothrombotic state [22], and there is an increase in fibrinolysis, especially in the uterus at the time of placental separation [23, 24]. The platelet count may fall during pregnancy (gestational thrombocytopenia), although this is rarely to a level that significantly contributes to the risk of bleeding.

Haemostatic changes

There is an increasing evidence that the haemostatic impairment associated with bleeding in the pregnant population is different from trauma-induced bleeding, and furthermore the type and time of onset of coagulopathies differs with the underlying cause of obstetric bleeding (Table 1).

Although haemostatic impairment may develop during PPH, in the majority of cases conventional coagulation studies (PT/aPTT) remain normal despite relatively large amounts of bleeding [25–27]. In a cohort of 456 women with PPH, most had normal PT/aPTT until blood loss reached 5000 ml. In contrast, the lowest fibrinogen value fell progressively as blood loss increased [26], as in other causes of massive haemorrhage, and therefore reaches critically low levels earlier than other coagulation factors [28].

The type, severity and rate of onset of coagulopathy vary with the aetiology of the bleeding [12, 13]. Uterine atony, surgical and genital tract trauma-induced bleeding is often associated with no significant coagulopathy, even with relatively large blood loss [27]. However, if bleeding is not controlled, a predominantly dilutional coagulopathy may evolve. In contrast, placental abruption may be associated with a severe and rapid consumptive coagulopathy characterised by hypofibrinogenaemia and thrombocytopenia, with clinically severe haemostatic impairment, despite minimal blood loss initially [13]. Amniotic fluid embolus is associated with a severe and rapid disseminated intravascular coagulation (DIC) [13, 29]. The fibrinogen level after 1000–1500 ml PPH due to uterine atony, genital and surgical trauma and retained or adherent placenta was, on average, 3.9 g.l^{-1}, and PT and aPPT were normal in 98.4% and 98% of cases, respectively. In placental abruption, the average fibrinogen was 2.2 g.l^{-1} whilst the PT/aPTT ratios were normal in all cases [27]. This demonstrates that different aetiologies have variable effects on fibrinogen, but not other coagulation factors, despite the volume of PPH being the same.

Coagulopathies may develop secondary to the dilution of coagulation factors during resuscitation [28]. Volume replacement leads to the dilution of all coagulation factors, which affects thrombin generation and also leads to a fall in fibrinogen levels and platelet counts, affecting clot strength. The use of colloids, especially the hydroxyethyl starches, may further interfere with fibrin clot strength [30].

Table 1 Mechanisms of coagulopathy dependent on aetiology of obstetric bleed. Late onset is abnormal coagulation usually only after 2000 ml blood loss.

			Mechanism of coagulopathy		
				Consumptive	
Aetiology of bleed	Likelihood of coagulopathy (% transfused FFP)	Time of onset of coagulopathy	Dilution	Local to uterus and placenta	Disseminated intravascular
Uterine atony	14	Late	Contributes in severe cases	Contributes in severe case	Very rare
Genital tract or surgical trauma	4	Late	Contributes in severe cases	Contributes in severe cases	Very rare
Placental abruption	42	Early (often before blood loss observed)	Contributes in severe cases	Main cause in mild and moderate cases	Contributes in severe cases
Retained and adherent placenta	8	Early or late	Contributes in most cases	Contributes in some cases	Rare unless associated with infection
Uterine rupture	66	Early	Main cause because large bleeds are common	Contributes in some cases	–
AFE	100	Early	Contributes in large bleeds	–	Main cause
Pre-eclampsia/HELLP	ND	Early (often before labour)	Contributes in large bleeds	Contributes in some cases	Contributes in some cases

AFE, amniotic fluid embolus; HELLP, haemolysis, elevated liver enzymes and low platelets.

Consumption results from dysregulated activation of coagulation and a reduction in coagulation factors, especially fibrinogen and platelets [12, 13, 31]. Although PPH is often thought to be associated with DIC, this is an uncommon event and very few cases fulfil internationally agreed criteria [12, 13, 27, 32, 33]. The consumptive coagulopathies associated with PPH are often localised to the placental bed (e.g. in many cases of abruption), or related to coagulation factors being consumed into inter-uterine clots (e.g. in atony) [12]. True DIC is seen with amniotic fluid embolus, in some cases of severe pre-eclampsia or HELLP syndrome and more severe cases of abruption [29]. Whether localised or disseminated, consumption leads to critically low levels of coagulation factors, especially fibrinogen, earlier than would occur with dilution alone. Local activation of the fibrinolytic system at the time of delivery [24] contributes to a reduction in stable clot formation.

There is limited information on haemostatic changes during evolving PPH [12]. One study measured serial coagulation factors during PPH and, although women who progressed to severe PPH had lower initial levels, there was remarkably little change in PT, fibrinogen, platelets, factor V and factor II over the time of the bleed in both severe and non-severe cases. By contrast, there was an early increase in thrombin/antithrombin complexes and D-dimer levels, indicating activation of coagulation and fibrin cross-linking in both groups. There was minimal change in plasmin/antiplasmin complexes suggesting limited ongoing activation of fibrinolysis. Only two women in this study suffered abruption, therefore it cannot be assumed that PPH of different aetiology would have the same findings [25]. Another study showed minimal changes in PT and aPTT values in most women despite blood loss of 5000 ml [26].

Role of fibrinogen

There has been increasing interest in hypofibrinogenaemia during PPH [34]. Fibrinogen levels fall below the normal pregnancy range sooner than other coagulation factors [26], and, in some circumstances, may rapidly fall to < 2 g.l^{-1} [13, 27]. There is strong evidence that a low Clauss fibrinogen is an accurate biomarker for progression from moderate to severe PPH [25, 27, 35–

37]. Importantly, these studies report the first fibrinogen value taken, although the timing of the testing varied depending on the entry criteria (Table 2).

Charbit et al. demonstrated that, in women recruited at the time of a second line uterotonic for resistant atony, a fibrinogen < 2 g.l^{-1} had a positive predictive value of 100% for progression to severe PPH, whilst a level > 4 g.l^{-1} had a negative predictive value of 79% [25]. A similar result was found by Cortet et al., although this study excluded all women with surgical bleeding or caesarean section [35]. Gayat et al. reported that fibrinogen < 2 g.l^{-1}, taken on average 4 h after the start of PPH, was an independent predictor of progression to the need for an invasive procedure, including iliac artery ligation, hysterectomy and admission to level three intensive care [37]. In a consecutive cohort of women with any cause of PPH, recruited when abnormal bleeding was identified at around 1000–1500 ml, a fibrinogen < 3 g.l^{-1}, and especially < 2 g.l^{-1}, was associated with progression to larger bleeds, more prolonged bleeds, higher rates of red cell and fresh frozen plasma (FFP) transfusion, and longer stays in high dependency care [27]. Poujade et al. found fibrinogen was an independent predictor of successful arterial embolisation, the mean (SD) fibrinogen level in the successful group was 2.89 (1.32), compared with 1.79 (0.9) in the unsuccessful group [38].

Although low fibrinogen is more commonly associated with specific aetiologies of bleeding, in the earlier stages of PPH from any cause it has similar predictive values. Combining studies in over 1700 women [25, 27, 35–37], it can be concluded that a fibrinogen < 3 g.l^{-1} and especially < 2 g.l^{-1}, in the early phase of the PPH, is associated with progression, whilst a fibrinogen > 4 g.l^{-1} is not (Table 2).

Monitoring haemostasis

There are three broad strategies for assessing haemostatic impairment during PPH. These are clinical observation combined with empirical, formulaic blood product replacement; and either laboratory-based PT/aPPT ratios and Clauss fibrinogen or point-of-care (POC) testing [12, 18].

Routine coagulation tests are the most common method for monitoring haemostasis during PPH, with the advantage of well-regulated quality control [12, 18]. Their main drawback is that they are too slow to be clinically useful in an acute and evolving situation. In addition, PT/aPTT ratios have limited sensitivity to a developing coagulopathy associated with PPH, and are often normal despite very large volumes of blood

Table 2 Clauss fibrinogen as a biomarker for predicting progression of postpartum haemorrhage (PPH). Values are median (IQR) or mean (SD).

Reference	Number studied	Entry criteria	Definition of progression	Fibrinogen level; g.l^{-1}	
				Non-progression	Progression
Charbit et al. [25]	128	Second line uterotonic after manual evacuation	Fall in Hb > 40 g.l^{-1}, ≥ 4 units RBC, need for invasive procedure*	4.4 (3.7–5.1)	3.3 (2.5–4.2)
Cortet et al. [35]	738	Vaginal delivery > 500 ml PPH Excluding genital tract trauma, uterine rupture, accreta and praevia	Fall in Hb > 40 g.l^{-1}, any red cell transfusion, need for invasive procedure, admission to ICU	4.2 (1.2)	3.4 (0.9)
Gayat et al. [37]	257	Admission to referral centre for PPH†	Need for an invasive procedure	2.65 (2.08–3.46)†	1.8 (1.09–2.52)†
De Lloyd et al. [36]	240	Any cause of PPH and time of first coagulation test	Need for ≥ 4 units red cells or PPH > 2500 ml	4.4 (1.1)	3.1 (1.0)
Collins et al. [27]	346	Any cause of PPH 1000–1500 ml	Need for ≥ 4 units red cells or PPH > 2500 ml	3.9 (3.2–4.5)	2.8 (2.1–3.8)

*Most defined as progressing based on fall of Hb > 40 g.l^{-1}.
†Fibrinogen was taken on average 4 h after the onset of bleeding on admission to a referral centre and this contributes to the lower fibrinogen levels in this cohort.

loss [26, 27]. If laboratory-based tests are used, a Clauss fibrinogen must be measured rather than a PT-derived fibrinogen level.

Point-of-care testing of coagulation using thromboelastography (TEG®; Haemonetics, Braintree MA, USA), or thromboelastometry (ROTEM®; TEM GmBH, Munich, Germany) is uncommon on the delivery suite, despite their introduction in a number of other clinical areas that require rapid assessment of haemostasis. A review of the technology behind the devices and interpretation of results has been published [18]. Thromboelastometry normal ranges at the time of delivery differ from the non-pregnant normal range. The MCF/MA are larger and CT/r-time shorter, which has to be taken into account during interpretation [18, 20, 21].

There is good evidence that the ROTEM FIBTEM A5 assay (available within 10 min) can be used as a surrogate for Clauss fibrinogen during PPH [18, 19, 27, 39]. It is important to recognise that this assay does not measure the same haemostatic parameter as Clauss fibrinogen, but provides similar measures of haemostatic competence [27]. As a rough guide, a FIBTEM A5 of 15 mm equates to a Clauss fibrinogen of about 3 $g.l^{-1}$, 10 mm to 2 $g.l^{-1}$, and 6 mm to 1 $g.l^{-1}$, although with moderate variability (r value = 0.6). Some units use TEG and report that it contributes to clinical care (C Elton, personal communication), but outcome data have not been published [18, 21].

There are no studies that compare the use of coagulation screens and thromboelastometry during PPH, although it might be assumed that an earlier result using it would be beneficial. The major advantage of POC testing is that the obstetric and anaesthetic team can rapidly identify whether the bleeding has a purely obstetric cause, with normal coagulation for pregnancy, or if the bleeding is being exacerbated by abnormal haemostasis.

Intervention triggers

A summary of current guidelines is shown in Table 3. Current obstetric haemorrhage guidelines are extrapolated from studies in trauma-induced bleeding, and there are no data to support their use in PPH. An abnormal PT/aPTT in the obstetric population indicates established and severe haemostatic impairment and the need for urgent action to correct the coagulopathy. Multiple studies now support the view that a fibrinogen of 1 $g.l^{-1}$ is too low for adequate haemostasis during ongoing obstetric bleeding, and that a minimum level of at 2 $g.l^{-1}$ may be more appropriate [10, 25, 27, 35–37].

Fresh frozen plasma

There are limited data to inform practice on the treatment of haemostatic impairment with FFP during PPH. Some centres have adopted formulaic protocols for the management of obstetric bleeding based on data derived from massive trauma. In some centres, 1:1 red cells:FFP [40] or other fixed ratio transfusion policies have been adopted [31], and some advocate the addition of platelets into a 1:1:1 protocol [41]. These products are frequently issued as 'shock packs' on activation of a major obstetric haemorrhage protocol. The rationale for this approach is to maintain thrombin generation and fibrinogen by the replacement of coagulation factors as early as possible, and that it takes too long in practice to obtain laboratory results and issue components.

The disadvantage of unmonitored 'shock packs' is that the majority of women will have completely normal coagulation and platelets at the time of administration, and will be receiving blood products with less fibrinogen and other coagulation factors than they have circulating. Fresh frozen plasma is donated from the non-pregnant population and has a fibrinogen level of around 2 $g.l^{-1}$, and will therefore, lead to a reduction in fibrinogen, factor VIII, and von Willebrand factor, due to dilution.

Current guidelines do not distinguish between the underlying aetiology of bleeding. Early empirical FFP might be justified if significant consumption is likely (e.g. placental abruption or amniotic fluid embolus), or very large volumes of blood loss are expected (e.g. uterine rupture or placenta accreta). By contrast, uterine atony or surgical/genital tract trauma are unlikely to have early haemostatic impairment and early unmonitored FFP administration is more difficult to justify.

In contradiction to the concept of early FFP, guidance also advocates a transfusion trigger of aPTT/PT ratios of 1.5× normal [8], or infusing FFP to prevent the PT/aPPT ratios reaching 1.5× normal [9]. Once

Table 3 Comparison of management strategies for postpartum haemorrhage.

	RCOG [8]	AAGBI	WHO [11]	NICE [10]	Authors' strategy
Primary monitoring	Coagulation screen	Coagulation screen	NA	NA	FIBTEM + coagulation screen
Support for point-of-care	Yes	Yes	NA	NA	Yes
Empirical FFP	1 l FFP for every 6 units red cells or > 4500 ml PPH	1 l if massive transfusion anticipated	NA	NA	Only in exceptional circumstances
Goal-directed FFP	15 ml.kg^{-1} if PT/aPTT > 1.5× normal	15 ml.kg^{-1} to prevent PT/aPTT becoming > 1.5× normal High volume if > 1.5× normal	NA	NA	15 ml.kg^{-1} if FIBTEM < 12 mm or PT/aPPT abnormal Higher volume if > 1.5× normal
Fibrinogen	2 pools cryoprecipitate if < 1 g.l^{-1} or if > 4500 ml PPH and blood tests not available	Cryoprecipitate or fibrinogen concentrate to maintain Clauss fibrinogen > 1.5 g.l^{-1}	NA	NA	Fibrinogen concentrate according to protocol based on POCT to maintain Fibtem > 11 mm
Platelets	< 50 × 10^9.l^{-1}	< 75 × 10^9.l^{-1}	NA	NA	< 75 × 10^9.l^{-1}
Tranexamic acid	No	Yes	Yes if second line uterotonics have failed or bleed due to trauma	Yes	Yes
Recombinant factor VIIa	In life-threatening bleeding if fibrinogen > 1 g.l^{-1} and platelets > 20 × 10^9 l^{-1}	Centres need agree protocols and fibrinogen should be normal	Insufficient evidence to give opinion	Yes if other coagulation factors normal	Exceptionally rarely used. Fibrinogen > 2 g.l^{-1} and platelets > 50 × 10^9 l^{-1}

RCOG, Royal College of Obstetricians and Gynaecologists; AAGBI, Association of Anaesthetists of Great Britain and Ireland; WHO, World Health Organization; NICE, National Institute of Health and Care Excellence. NA, no advice given.

the PT/aPPT ratios has reached 1.5× normal, very severe and established haemostatic impairment is present, and waiting until this has occurred is difficult to justify in our opinion; in our practice, we transfuse FFP if the PT/aPTT is at all abnormal. This is not addressed in current guidelines [10, 11].

A recent audit of an algorithm to manage obstetric haemorrhage (> 1500 ml and ongoing) based on FIBTEM A5 has been published. It showed that the use of fibrinogen concentrate in place of FFP/platelet 'shock packs' when the FIBTEM A5 fell below 7 mm (and considered if below 12 mm in clinically severe bleeding), led to a substantial reduction in transfused red cells, FFP, cryoprecipitate, platelets and transfusion-associated circulatory overload, and a non-significant reduction in hysterectomy [42]. These data support the use of POC testing during PPH, and are the first to provide evidence for a potentially appropriate intervention trigger (FIBTEM < 12 mm and/or fibrinogen of 2.2 g.l^{-1}). It also supports the practice of not giving haemostatic blood products if the bleeding has stopped, whatever the results. Importantly, this study shows that the use of 'shock packs' resulted in over-transfusion, even when supported by POC testing, and therefore the un-monitored use of shock packs is unlikely to be beneficial for the majority of women.

Cryoprecipitate

Guidelines recommend the use of cryoprecipitate to maintain the fibrinogen level above 1–1.5 g.l^{-1} if FFP has not been successful [8, 9]. Cryoprecipitate has been shown to successfully increase fibrinogen levels during PPH [43]. One pool of cryoprecipitate would be expected to raise the fibrinogen level by about 0.5 g.l^{-1} in the average woman, although this will vary depending on consumption. The dose should depend on the

measured and target fibrinogen level. Cryoprecipitate also contains a high concentration of factor VIII, von Willebrand factor and factor XIII, which will be depleted in established haemostatic failure.

Platelets

Guidelines recommend that the platelet count should be kept $> 50 \times 10^9.l^{-1}$ during ongoing PPH, and to achieve this they should be infused when the count falls below $75 \times 10^9.l^{-1}$ [8, 9]. With the exception of placental abruption, amniotic fluid embolus, severe pre-eclampsia, or inherited or immune thrombocytopenia, a platelet count $< 75 \times 10^9\ l^{-1}$ is uncommon during PPH. The strategy of 1:1:1 red cells:FFP:platelets transfusion would result in multiple platelet transfusions well above recommended levels and, in our view, cannot be justified on current evidence.

Tranexamic acid

This has been shown to reduce bleeding and transfusion requirement in massive haemorrhage secondary to a number of non-obstetric causes. Its role in obstetric bleeding is not established [44], and the Royal College of Obstetricians and Gynaecologists' guidelines state 'there is a consensus view that fibrinolytic inhibitors (such as tranexamic acid) seldom, if ever, have a place in the management of obstetric haemorrhage', although it is acknowledged that evidence is conflicting and this guidance is currently under review [8]. World Health Organization guidelines suggest using tranexamic acid in uterine atony if uterotonics fail to control bleeding or bleeding may be partly due to trauma [11], whilst NICE guidelines describe tranexamic acid as an additional option [10].

An open-label study of 144 women randomised to standard care with or without tranexamic acid after blood loss exceeding 800 ml, reported a reduction in blood loss, shorter period of bleeding and fewer women progressed to severe PPH or the need for blood transfusion. This study had limitations, because it was not blinded and relatively small numbers were involved, but showed a potential efficacy that needs further investigation in larger studies [45].

The double-blinded WOMAN study aims to investigate the role of tranexamic acid in early PPH. It is randomising 20 000 women after 500 ml blood loss to either tranexamic acid or placebo, with a primary endpoint of death or hysterectomy (www.thewomantrial.lshtm.ac.uk accessed 30/7/2014). This study will provide valuable information on the role of early tranexamic acid in reducing progression from mild to severe PPH. It is important to recognise, however, that the women enrolled in the WOMAN study will almost have normal coagulation at the time of randomisation. It is unlikely that the results can be translated to the treatment of severe PPH or to women with hypofibrinogenaemia, and the question of whether tranexamic acid is indicated in these cases is likely to remain unresolved.

Fibrinogen concentrate

Fibrinogen concentrate (RiaSTAP™; CSL Behring, King of Prussia, PA, USA) has been used to correct hypofibrinogenaemia during PPH, although this indication is unlicensed in many countries. The literature consists of case reports and series of women with significant hypofibrinogenaemia. It is easy to mix and administer in an acute situation, which has made it popular in some centres, and anecdotal, uncontrolled studies report improved clinical haemostasis associated with increased fibrinogen levels [43, 46–49]. Increasing the fibrinogen level by $1\ g.l^{-1}$ requires about $60\ mg.kg^{-1}$ fibrinogen [47], although if there is ongoing consumption or dilution, smaller increments would [43] be expected.

Fibrinogen concentrate infused on the basis of a reduced FIBTEM significantly reduced blood product usage and fluid overload compared with the use of shock packs. Of interest, this study showed that targeted fibrinogen concentrate administration resulted in a lower total amount of fibrinogen being administered [43].

There are currently four prospective, randomised studies investigating the role of fibrinogen concentrate in PPH [50] (www.clinicaltrials.gov NCT01359878, NCT02155725, and NCT01910675; and www.isrctn.org ISRCTN46295339).

Prothrombin complex concentrate

Prothrombin complex concentrate contains clotting factors II, IX and X ± VII, and are occasionally used off-label during PPH. A study is currently investigating

their role, in combination with fibrinogen concentrate, during severe PPH (NCT01910675). Prothrombin complex concentrate may be associated with thrombotic events in the non-obstetric population and, given the current lack of evidence to support their use in PPH, we do not recommend their use outside clinical trials because their side-effects may outweigh their benefits.

Recombinant factor VIIa

There has been interest in recombinant factor VIIa (NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark) to treat life-threatening PPH or to prevent hysterectomy [31], although the manufacturer does not recommend its use in such a setting. The Royal College of Obstetricians and Gynaecologists suggests that NovoSeven may be used in the face of life-threatening PPH, and recommends that the fibrinogen level should be > 1 g.l^{-1} and platelet count $> 20 \times 10^9$.l^{-1} [8]. Although there are no data to support or refute these recommendations, circumstantial evidence suggests that a higher fibrinogen and platelet count may be necessary. The National Institute for Health and Care Excellence recommend that other coagulation factors should be normal before considering administering NovoSeven [10]. The data available are anecdotal case reports or registries, and are inevitably prone to significant reporting bias. The World Health Organization argues that is not possible to make any meaningful conclusions from the literature [11], and clinical trials are the only feasible way forward.

Pragmatic management

In view of the contrasting guidelines and emerging data, the following section describes how we currently treat PPH in Cardiff.

Delivery suite staff are trained to activate the Major Obstetric Haemorrhage protocol after 1000 ml blood loss. This ensures that the senior midwifery, obstetric and anaesthetic staff are all involved in optimising obstetric management and providing early resuscitation. As the likelihood of haemostatic impairment is related to the underlying cause of PPH and the volume of blood loss, a measured, rather than estimated, blood loss is recorded in all areas of the delivery suite, including the midwifery unit [51], because visual estimation has been shown to be inaccurate [52]. The majority of bleeding patients are controlled without any red cells or blood products at this stage.

On activation of the major obstetric haemorrhage protocol, blood samples are taken for a FIBTEM assay, a point-of-care Hb measurement, and a full blood count and coagulation screen (laboratory). To make interpretation simple, we assume that if the FIBTEM is ≥ 16 mm (equivalent to a fibrinogen level of about 3 g.l^{-1}), then all other coagulation factors will be normal and no FFP or cryoprecipitate is required [27]. The focus is then entirely on the obstetric management and monitoring of the mother's cardiovascular status. The FIBTEM and coagulation screen are repeated at the discretion of the treating clinicians with blood and blood products ordered depending on the evolving clinical situation.

The majority of PPH is caused by atony and trauma, which is not commonly associated with early abnormalities of coagulation factors or a low fibrinogen level. Prompt obstetric intervention usually controls the PPH without the need for coagulation products. We do not use empirical early FFP, even for abruption or amniotic fluid embolus, because the FIBTEM is available after 10 min. If the woman is not actively bleeding, then we do not infuse any plasma components, whatever the coagulation test results. Blood bank issues red cells based on measured ongoing blood loss and Hb. Fresh frozen plasma is not ordered if FIBTEM is > 15 mm, is defrosted if FIBTEM is between 12 and 15 mm with ongoing bleeding but not transported to delivery suite unless specifically instructed, and automatically transported if FIBTEM is < 12 mm and bleeding is ongoing. If PT/aPTT ratios are abnormal, we give an extra 15 ml.kg^{-1} FFP, if PT/aPTT ratios are > 1.5 then an increased dose of FFP is given after discussion with haematology colleagues. We infuse platelets if the count $< 75 \times 10^9$ l^{-1} and do not use any empirical platelet transfusions. We now use fibrinogen concentrate to manage severe monitored coagulopathy if FFP has failed. If bleeding stops after administration of fibrinogen concentrate, additional FFP is not given, because this may cause dilution of plasma fibrinogen and fluid overload (Fig. 1). A similar strategy based on cryoprecipitate could be used by centres that do not elect to use off-label fibrinogen concentrate. We also administer 1 g tranexamic acid if

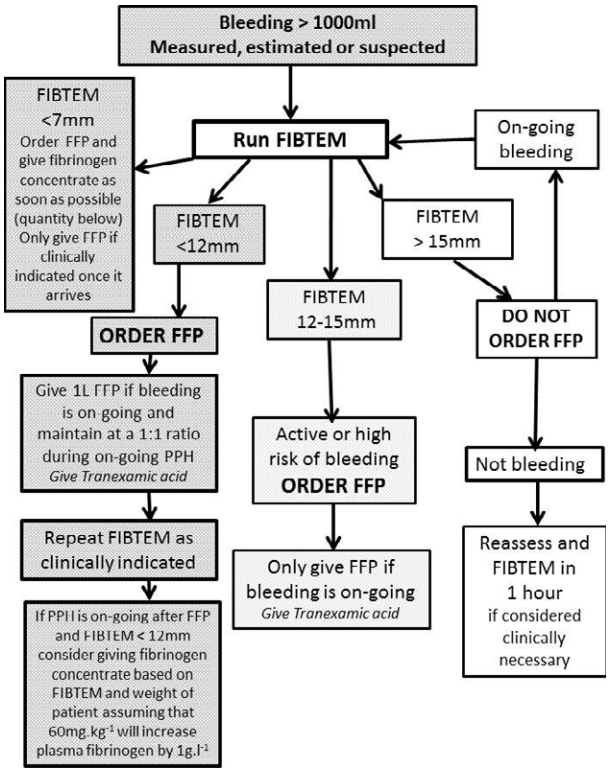

Figure 1 Point-of-care FIBTEM algorithm used at The University Hospital of Wales in 2014. PPH, postpartum haemorrhage; FFP, fresh frozen plasma.

bleeding is not controlled by initial obstetric interventions and especially if there is evidence for haemostatic impairment.

Changes to the haemostatic management of PPH in our centre are the result of initiatives based on local audits and discussions at clinical risk meetings. There is evidence that our rate of pulmonary oedema secondary to PPH, hysterectomy rates and admission to level-3 ICU has gradually fallen over the last five years [53, 54]. More recently, we have also reduced our blood and blood product usage in a very similar way to the Liverpool experience ([43]), after the introduction of POC testing, despite not routinely giving fibrinogen concentrate.

Conclusion

A fibrinogen level of < 3 g.l^{-1} and especially < 2 g.l^{-1} is associated with large, more significant bleeds; therefore, the current guidance to keep fibrinogen > 1 or 1.5 g.l^{-1} would appear to be too low. The formulaic approach to management with shock-packs does not take into account that in the majority of PPH, the mother's fibrinogen level will be greater than that in the FFP administered, and therefore unmonitored usage will lead to dilution and possibly contribute to pulmonary complications. Point-of-care testing allows real time monitoring and a tailored approach to coagulopathy management. Monitored administration of fibrinogen concentrate has led to a fall in blood product usage, but the results of trials are required before recommendations on its routine use can be made.

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Competing interests

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Review Article

Management of peri-operative anti-thrombotic therapy

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Summary

The management of antithrombotic therapy in the peri-operative setting is a common problem, balancing haemorrhagic risk with continued treatment and thrombotic risk when discontinued. High-quality evidence is lacking regarding the optimal approach for patients on oral anticoagulants or antiplatelet agents. This review discusses the available evidence for the management of patients on warfarin, non-vitamin K antagonist oral anticoagulant drugs, and antiplatelet therapy in the peri-operative setting. Bridging therapy for patients on warfarin should be considered for those at highest risk of thrombosis, whereas it may not be necessary for those on non-vitamin K antagonist oral anticoagulant drugs given the reduced time off anticoagulation and their more predictable pharmacokinetics. Aspirin can be continued for most procedures. Dual antiplatelet agents for patients with a recently inserted coronary artery stent should be continued if possible but decisions should be individualised and taken after multidisciplinary discussion.

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Introduction

Bridging anticoagulation refers to the temporary interruption of oral anticoagulation and introduction of a short acting anticoagulant such as low molecular weight heparin or unfractionated heparin, to allow surgical or invasive procedures. There is no consensus regarding the optimal peri-operative strategy [1, 2], and it is dependent on the bleeding risk, the consequences of bleeding, the thrombotic risk associated with stopping anticoagulation and its consequences, as well as the effectiveness of a bridging protocol [3]. The uncertainty is related to the lack of randomised controlled trials. There is increasing evidence from systematic reviews and meta-analyses that bridging therapy is associated with an increased risk of bleeding, Whilst the absolute reduction in thrombotic events is uncertain [4–6], and because of this various bridging therapy protocols are in use.

The time for interruption of non-vitamin K oral anticoagulants is shorter, due to their reduced half-life, making bridging potentially unnecessary [7]. However, there are only limited data available on the optimal peri-operative management of patients on non-vitamin K antagonist oral anticoagulant drugs. In addition, there are concerns related to varying pharmacokinetics, limited data in patients with severe renal impairment, variability in routine coagulation tests to demonstrate the presence of therapeutic levels of anticoagulation with non-vitamin K antagonist oral anticoagulant drugs, and the absence of specific reversal agents. Therefore, some expert groups suggest a longer period of interruption and bridging [8, 9].

The optimal peri-operative management of patients with coronary stents on antiplatelet agents is equally uncertain, and recommendations vary widely as to when it is safe to perform surgery in this group,

which antiplatelet agents should be stopped, and when [10].

In this review, we discuss the thrombotic and haemorrhagic risks related to interruption or continuation of antithrombotic therapy in the peri-operative period and summarise the evidence for bridging anticoagulation in patients on warfarin. We also provide practical suggestions on the use of antithrombotics in the peri-operative setting based on international guidelines. Bridging in this paper refers to the peri-operative use of intermediate or therapeutic doses of low molecular weight heparin or unfractionated heparin, as opposed to thromboprophylactic doses.

Thrombotic risk

The guidelines of the American College of Chest Physicians stratify patients into the following thrombotic risk categories:

- High risk (> 10% risk of thrombotic events per year)
- Moderate risk (5–10%)
- Low risk (< 5%)

High-risk patients should be considered for bridging; moderate-risk patients may be considered for bridging in non-high risk for bleeding procedures; whereas low-risk patients do not require bridging [3]. The guidelines of the British Committee for Standards in Haematology use a two-tiered approach, and suggest that patients in the high-risk group should be considered for bridging [11].

Atrial fibrillation

The risk of stroke in non-valvular atrial fibrillation can be estimated by the CHADS2 score [12, 13] and CHA2DS2-VASc score [14, 15]. Although not validated in the peri-operative setting, the CHADS2 score is used to stratify thrombotic risk, enabling decisions on bridging by following the American College of Chest Physicians' guidelines [3]. The CHADS2 score is calculated by scoring one point for congestive heart failure, hypertension, age ≥ 75 years or diabetes mellitus, and two points for previous stroke or transient ischaemic attack. Low-risk patients include those with a CHADS2 score 0–2, moderate-risk with CHADS2 score 3–4, and high-risk with a CHADS2 score of 5 or 6. This, however, does not take individual patient factors into account. The British Committee for Standards in Haematology suggests that patients with a prior transient ischaemic attack or stroke should be regarded as high risk, and that bridging may also be considered in patients without prior transient ischaemic attack or stroke who have multiple other risk factors, without further specifying these [11]. Another high-risk group is patients with rheumatic valvular heart disease [16].

Venous thrombo-embolic events

The risk of recurrent venous thrombo-embolic events (VTE) is highest if anticoagulation is discontinued within 3 months of a thrombotic event [17], and is > 10% per year [3]. Other groups at increased risk of recurrence are patients on anticoagulation for cancer-associated VTE with an estimated annual risk of recurrence of 15% [3], but it is probably higher in patients with rapidly progressing/metastatic cancer [18]; and patients with antiphospholipid syndrome who are at risk of both arterial and venous thrombosis [19, 20]. Patients with inherited antithrombin deficiency may be considered for peri-operative treatment with antithrombin concentrates [21, 22], and this should be discussed with a haematologist pre-operatively.

Both the US and UK guidelines classify VTE within the last 3 months as high risk [3, 11]. We suggest these patients should be considered for bridging, as well as patients with antiphospholipid syndrome. Most patients with VTE more than 3 months previously should receive thromboprophylaxis with low molecular weight heparin until the International Normalised Ratio (INR) is at therapeutic levels [11]. On an individual basis, we would consider intermediate doses of low molecular weight heparin in patients with previous VTE (more than 3 months before) and protein C or S deficiency, combined heritable thrombophilias or active metastatic cancer.

Prosthetic heart valves

Data on the risk of valve thrombosis or embolism in patients with mechanical heart valves in whom anticoagulation is interrupted are limited. A meta-analysis suggested a 4% risk of major embolism and 1.7% risk

of valve thrombosis in patients not on anticoagulation. The valve position was not specified, but for anticoagulated patients, the risk of major embolism was approximately double for mitral valve compared with aortic valve prosthesis [23]. Overall, the analysis contained predominantly patients with aortic valve prostheses, or the position was unknown [23]. The British Committee for Standards in Haematology estimate the risk of thrombosis to be 12% per year for mechanical mitral valve prostheses and 4% per year for mechanical bileaflet aortic valve prostheses without atrial fibrillation or other risk factors for stroke [11]. The American College of Chest Physicians classify mechanical mitral valve prostheses, any mechanical valve and recent (within 6 months) stroke or transient ischaemic attack and patients with caged-ball or tilting-disc aortic prostheses as high risk; bileaflet aortic prosthesis and atrial fibrillation or other risk factors for stroke moderate risk; and bileaflet aortic valve prostheses without atrial fibrillation or other factors for stroke low risk [3]. The British Committee for Standards in Haematology suggests that patients with a mechanical mitral valve should be considered for bridging, whereas patients with bileaflet aortic valves without other risk factors for stroke are considered to be at low risk [11]. They have not assessed other situations. For simplicity, we suggest that all patients with mechanical valves except those with aortic bileaflet valves without other risk factors for stroke should be considered for bridging.

Thrombotic risk related to surgery

The type of procedure also significantly influences the thrombotic risk. A retrospective study of a population-based linked administrative database of hospitalised patients found the 30-day risk of postoperative stroke to be 1.8% (95% CI 1.7–1.9%) in patients with atrial fibrillation vs 0.6% in those without (95% CI 0.58–0.62%). After risk adjustment, the odds ratio (OR) for stroke in patients with chronic atrial fibrillation was 2.1; highest after neurosurgery (OR 2.9) and vascular surgery (OR 2.4) and lowest after coronary artery bypass graft (OR 1.4), valve surgery (OR 1.3) and lung surgery (no difference). The CHADS2 score was an independent risk factor for stroke [24].

The million women study found a 70-fold increased risk of VTE related to inpatient surgery (highest after hip and knee replacement with OR 220 and cancer surgery with OR 96), and a 10-fold increase after day-case surgery, compared with women who did not have surgery [25]. Finally, patients with cancer on anticoagulation for previous VTE were found to have a significantly higher risk of recurrence in the 3 months following surgery compared with patients without cancer (2.1% vs 0.2%) [26].

Procedure-related haemorrhagic risk

Given the thrombotic risks associated with interruption of anticoagulation, performing surgery on patients without stopping Vitamin K antagonist drugs should be considered. Evidence for interventions in patients on warfarin therapy is available for joint injections [11], cataract surgery [12, 27], minor dental procedures [3, 28], minor dermatological procedures [3] and some endoscopic procedures [29]. Increased bleeding has been demonstrated for some procedures, but this is usually minor and self-limiting and does not outweigh the risk of thrombo-embolic events. Patients should be made aware of the possibility, and administration of antifibrinolytic drugs, such as tranexamic acid, should be considered [28].

For pacemaker and defibrillator surgery, continuation of warfarin therapy may be preferable to bridging anticoagulation in patients at moderate or high thrombotic risk [30, 31]. The Bruise Control trial [30] showed clinically significant device pocket haematoma in 16% of patients who were randomly assigned to bridging (therapeutic doses of heparin started 24 h pre-operatively) and 3.5% in patients who continued warfarin ($p < 0.001$). There were two strokes in atrial fibrillation patients in the warfarin group with a sub-therapeutic INR before the procedure [30]. Similarly, the European Society for Cardiology suggests that catheter ablation [32] and percutaneous coronary interventions [33] may be considered in high-risk atrial fibrillation patients while on warfarin therapy.

Warfarin therapy should be interrupted for procedures with a high risk of bleeding. These include procedures associated with extensive tissue damage, surgery in highly vascular organs, bowel resection with

risk of bleeding at anastomotic sites, cardiac, neurological and spinal surgery, urogenital tract surgery and more minor procedures associated with a high risk of bleeding, such as broad-based colonic polyp resection and renal biopsies [3].

The effectiveness of bridging

Although there are many studies assessing bridging, including various prospective cohort studies, there is only one randomised controlled trial, in dental procedures [34]. The studies vary in patient characteristics, bridging protocol, follow up and definitions of outcome. Overall, patients at high risk for thrombotic events are under-represented. For example, Dunn et al. described overall major bleeding rates of 3.5% and a thrombotic complication rate of 1.9% [35], however, the bleeding rate was 20% in patients undergoing major surgery. Therapeutic doses of low molecular weight heparin in this study were started between 12 and 24 h after the procedure and follow up was for 28 days [35]. Another study showed 13% major and clinically significant, but non-major bleeding, in bridged patients, and 0.8% in unbridged patients after minor procedures, but the time of restarting low molecular weight heparin was not given [36]. In contrast, Douketis et al. described significantly less major bleeding (1.8%) after high-risk procedures and a thrombotic rate of 1.8% [37]. However, only patients having non-high-risk procedures for bleeding had postprocedural low molecular weight heparin (100 $U.kg^{-1}$ 12-hourly, starting 24 h after the procedure), whereas patients in the high bleeding-risk group did not receive bridging. Follow up was a median of 13.8 days [37]. Others used intermediate doses of low molecular weight heparin as bridging to reduce the postoperative bleeding rate. Pengo et al. used an intermediate dose of 70 anti Xa $U.kg^{-1}$ in patients at high risk of thrombotic events, and prophylactic doses in those at moderate or low thrombotic risk. Overall major bleeding was 1.2%, 2.7% in those undergoing major surgery receiving low molecular weight heparin bridging. Major bleeding was significantly associated with the use of intermediate dose low molecular weight heparin (OR 4.6, $p = 0.047$) and follow up was 30 days [38]. A recent meta-analysis of 34 studies, including 7118 bridged and 5160 non-bridged patients, showed no significant difference in thrombotic rates (0.9% in bridged patients and 0.6% in non-bridged patients), but significantly increased bleeding rates (overall bleeding of 13.1% and major bleeding of 4.2% in bridged patients and 3.4%/0.9% in non-bridged patients, respectively) with an OR of 3.6 for major bleeding in bridged patients [6]. Another recent meta-analysis has shown similar results [4]. However, given the heterogeneity of individual studies and the under-representation of high-risk patients, it is possible that bridging is effective in the latter group. This is being evaluated in two randomised controlled trials, expected to be completed in March 2015 (the PERIOP2 trial (clinicaltrials.gov: NCT00432796) and the BRIDGE trial (clinicaltrials.gov: NCT00786474)).

Type, dose and timing of periprocedural anticoagulation

Most bridging protocols use low molecular weight heparin [6] because this is significantly more cost effective when used in the outpatient setting than in-patient unfractionated heparin-based protocols [39, 40], but there are no large prospective studies comparing agents. A registry study in 2006 found that they were similar in terms of thrombotic and haemorrhagic events [41]. A recent cohort study in patients with mechanical heart valves, mostly bileaflet aortic valves, found no significant difference in thrombotic events, but a significantly increased bleeding rate in patients bridged with unfractionated heparin (15.4% vs 5.4%, $p < 0.005$) [42]. We therefore suggest using low molecular weight heparin in most cases, but unfractionated heparin should be considered in patients with renal impairment because low molecular weight heparin is renally excreted. If low molecular weight heparin is used in patients with a creatinine clearance of < 30 $ml.h^{-1}$, dose reduction and monitoring of anti Xa levels should considered.

Dose and timing of bridging anticoagulation

Four doses should be omitted to reduce the INR to ≤ 1.5 in patients taking warfarin with a target INR of 2.5 [43]. While prophylactic doses of low molecular weight heparin are effective in preventing recurrent VTE in patients with a previous VTE (more than 3 months before a procedure) [44, 45], there is

no strong evidence that these prevent arterial thrombosis. Therefore, many bridging protocols use therapeutic doses of low molecular weight heparin in high-risk patients with AF and mechanical heart valves, as well as in patients with a recent VTE (< 3 months). The bleeding risk before a procedure is low, and most protocols start therapeutic doses of low molecular weight heparin either 2 or 3 days in advance, and the last dose should be given 24 h before [3, 11]. If possible, the INR should be checked on the day before the procedure, enabling vitamin K to be given if the INR is ≥ 1.5, thus avoiding cancellation due to a high INR on the day of surgery [11, 46].

Postoperatively, given the association between bridging and haemorrhagic complications, therapeutic doses of heparin should not be given shortly after surgery because low molecular weight heparin has been associated with a 20% bleeding rate when given within 12 and 24 h of major surgery [35]. Initiation of low molecular weight heparin therapy at 24 h was an independent risk factor for major bleeding and doubled the risk compared with starting it 48 h or later [47].

Given this, guidelines suggest that postoperative bridging with therapeutic doses should not be re-started within 48–72 h after high bleeding-risk procedures [3, 11], and only if there is no concern of bleeding following clinical review. Alternatively, reduced doses, or no bridging at all, should be considered until the concern has subsided. In low bleeding-risk procedures, therapeutic anticoagulation may be re-started 24 h after the procedure [3]. Warfarin can be re-started on the evening after the procedure or the following day [3], and low molecular weight heparin should be stopped when the INR is within the therapeutic range. Figure 1 describes a practical approach to bridging in high-risk patients that we use in our institution.

Emergency surgery

Warfarin can be reversed with vitamin K and prothrombin complex concentrate (PCC), or fresh frozen plasma when PCC is not available. We refer to a recent review for further information on emergency reversal of anticoagulation due to vitamin K antagonists [46].

Pre-operative management for patients at **high thrombotic risk**

Day -5	Day -4/-3	Day -2	Day -1	Surgery
Last dose of warfarin	Omit warfarin	Check INR: -If greater than 2 give 1 mg vit K orally and recheck day -1 - If 1.5 – 2.0 give1 mg oral vit K and recheck day -1. Start on dalteparin 100 U.kg^{-1} twice daily - If equal or less than 1.5 start on dalteparin 100 U.kg^{-1} twice daily	Recheck INR if greater than 1.5 on day -2 and give 1 mg vit K if greater than 1.5 Last dose of 100 U.kg^{-1} dalteparin in the morning (24 hours before surgery)	Check INR if greater than 1.5 on day -1

Postoperative warfarin management for patients at **high thrombotic risk**

Surgery	D +1	D+2	D+3	D+4	D+5	D + 6
Prophylactic dalteparin once a day by weight start 6 – 8 hrs post op	Warfarin at usual dose Continue prophylactic dalteparin		Warfarin at usual dose. Increase to twice daily prophylactic dalteparin		Warfarin at usual dose. Increase dalteparin to 100 U.kg^{-1} twice daily. Continue until INR is greater than 2.0	

Figure 1 High-risk bridging guidance as used in the author's institution.

Non-vitamin K antagonist oral anticoagulant drugs in the peri-operative period

It has been suggested that procedures that can safely be performed while patients are on warfarin may also be performed when patients continue on non-vitamin K antagonist oral anticoagulant drugs [48, 49]. The Dresden prospective registry reported 863 surgical procedures in 2179 patients [50]. Seventy-six per cent of patients were receiving rivaroxaban, 23.5% dabigatran and 4% apixaban. Ninety per cent of patients had relatively minor procedures including superficial skin and oral mucosal surgery, skin biopsy, wound revisions, transluminal cardiac, arterial, and venous interventions, pacemaker surgery, pleural and ascitic taps, cataract surgery, endoscopy, and dental extractions. Major bleeding was rare (0.5%), as were thrombotic events (0.8%). Non-vitamin K antagonist oral anticoagulant drugs were continued in 187 cases (21.7% overall), but there is no information in which specific procedures it was continued [50]. Therefore, even though it may be possible to continue non-vitamin K antagonist oral anticoagulant drugs in some procedures, we suggest that, until more information becomes available, these should be performed when serum levels are lowest or, omit one dose and restart medications after the procedure, provided there are no concerns regarding bleeding.

Pre-operative period

Non-vitamin K antagonist oral anticoagulant drugs have more predictable pharmacodynamics, a faster

onset of action and a shorter half-life than warfarin. Their half-life is dependent on renal function, as well as liver function for apixaban and rivaroxaban. Their mechanism of action, indications, dosage regimens and pharmacokinetic properties are summarised in Table 1. Because of their more predictable profile, the duration of interruption of anticoagulation is potentially shorter. In a post hoc analysis of the RELY trial, warfarin was stopped a median (range) of 114 (87–144) h before procedures, as compared with 49 (35–85) h for dabigatran, without differences in major bleeding or thrombotic events [7]. The mean duration of interruption in the Dresden non-vitamin K antagonist oral anticoagulant drug registry was 2 days pre-procedure and 1 day postprocedure [50]. There are, however, several issues that make the optimal pre-operative approach uncertain.

- Inter-individual variability in pharmacokinetics, variable data on half-life and limited data in patients with severe renal impairment [9, 51–58].
- The anticoagulant effect of non-vitamin K antagonist oral anticoagulant drugs cannot be quantified using routine coagulation tests [59–64].
- There are no specific reversal agents [65].

These issues have given rise to very different recommendations in the pre-operative management of non-vitamin K antagonist oral anticoagulant drugs from different expert groups. The summary of product characteristics for different drugs varies [51–53], and some expert groups use this guidance with minor alterations for major surgery [49, 66], whereas others, because of the above variables, suggest stopping anticoagulation with all non-vitamin K antagonist oral anticoagulant drugs 5 days before surgery where there is a high bleeding risk. They also suggest considering bridging with low molecular weight heparin in patients at high thrombotic risk, or stopping 2 days before minor procedures without bridging [8, 9]. This approach is potentially problematic in patients with renal impairment who may have significant residual levels of non-vitamin K antagonist oral anticoagulant drugs and may become over-anticoagulated when bridged with low molecular weight heparin. Increased bleeding related to bridging was found in the Dresden registry [50]. Anticoagulation was interrupted in 78% of all patients. Of these, 23% were bridged using therapeutic doses of heparin, predominantly when major surgery was being performed. There was significantly more major bleeding in the bridged patients (2.7% vs 0.5% in non-bridged group, $p = 0.01$ in major surgery), without a reduction in thrombotic events (0.8% vs 1.6%, respectively, $p = 0.265$).

We feel a rational approach is to omit a drug for two to three half-lives before minor surgery and four to five half-lives before major surgery, and use the upper limit of the half-life to calculate the time off each individual drug without using bridging anticoagulation. This approach was suggested in a recent publication [57]; a practical approach using this algorithm is shown in Fig. 2.

Postoperative period

Given the experience with bridging anticoagulation using heparins and the increased risk of bleeding in the immediate postoperative period, full anticoagulation with non-vitamin K antagonist oral anticoagulant drugs should be avoided for at least 48–72 h following high bleeding-risk procedures, and 24 h following low-risk procedures [57, 66]. In the intervening period, prophylactic low molecular weight heparin may be given. Some also consider anticoagulation with prophylactic doses of non-vitamin K antagonist oral anticoagulant drugs until full anticoagulation is resumed [57], but this is unlicensed except after total hip or knee replacement surgery. Renal and liver function should be checked before non-vitamin K antagonist oral anticoagulant drugs are re-started.

Emergency surgery

All efforts should be made to elicit the timing of the last dose of the anticoagulant drug. If at all possible, surgery with a high bleeding risk should be postponed for at least one to two half-lives of the drug. If possible, and the patient is on therapeutic anticoagulation, anti Xa levels for apixaban and rivaroxaban and diluted thrombin time (such as the Hemoclot assay) for dabigatran should be measured. Rivaroxaban prolongs the prothrombin time (PT) more than the activated partial thromboplastin time (aPTT), and dabigatran the aPTT more than the PT. Some suggest that a normal value of PT or aPTT mean that thera-

Table 1 Data based on manufacturers' summary of product characteristics for non-vitamin K oral anticoagulant drugs [51–53]. For the half-life data, additional information has been used from additional studies and review articles [54–58, 92].

	Mechanism of action	Licensed UK Indication	Dose	T_{max} (h)	Clearance	Half-life	Removable by dialysis
Dabigatran Contra-indicated if CrCl < 30ml.min^{-1}	Direct thrombin inhibitor	Stroke prevention in non-valvular AF Treatment of DVT/PE, prevention of recurrent DVT/PE	110 or 150 mg twice a day	0.5–2	80% renal	CrCl > 80: ≈13 h CrCl 50 to < 80: ≈15 h CrCl 30 to < 50: ≈18 h CrCl < 30: ≈27 h	Yes
Rivaroxaban Contra-indicated if CrCl < 15 ml.min^{-1}, use with caution if CrCl 15–29 ml.min^{-1}	Direct factor Xa inhibitor	Stroke prevention in non-valvular AF Treatment of DVT/PE, prevention of recurrent DVT/PE	15 mg bid in the first 21 days of VTE treatment 15 or 20 mg once per day in long-term VTE or AF treatment	2–4	66% metabolic including hepatobiliary, 33% direct renal excretion	5–13 h	No
Apixaban Contra-indicated if CrCl < 15 ml.min^{-1}, use with caution if CrCl 15–29 ml.min^{-1}	Direct factor Xa inhibitor	Stroke prevention in non-valvular AF Treatment of DVT/PE, prevention of recurrent DVT/PE	5mg BID or 2.5mg BID in long term treatment of AF. Treatment for venous thrombosis: 10mg BID for 7 days followed by 5mg BID and 2.5mg BID for long term prevention (after 6 months)	3–4	Multiple routes including hepatobiliary, 27% renal	7–15 h, CrCl 30–49 ml.min^{-1}: 17.6 h CrCl < 30 ml.h^{-1}: 17.3 h	No

CrCl; creatinine clearance; AF, atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism; AF, atrial fibrillation.

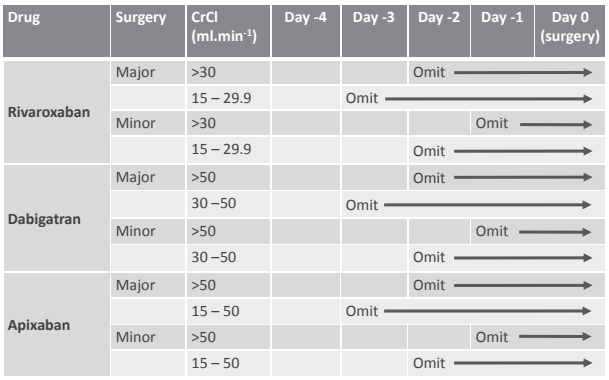

Figure 2 Suggested approach to interrupting individual non-vitamin K antagonist oral anticoagulant drugs before invasive procedures, based on half-life.

peutic anticoagulation with these drugs is unlikely [59, 60], but their sensitivity is highly dependent on the laboratory reagents used. Specific knowledge of the reagents used in individual laboratories is needed to interpret the results because a normal coagulation time does not exclude therapeutic anticoagulation in all patients on dabigatran or rivaroxaban [61, 63, 64]. The PT and aPTT should not be used to judge anticoagulation with apixaban [62]. A normal thrombin time excludes prophylactic dose levels of dabigatran.

Administration of activated and non-activated PCC and recombinant factor VIIa may be considered in the management of life-threatening bleeding in patients taking non-vitamin K antagonist oral anticoagulant drugs when other measures have failed [65], but their efficacy has not been established and these agents are not recommended for prophylaxis [9, 66, 67]. Haemodialysis may be considered in patients taking dabigatran [65].

Neuraxial anaesthesia is contra-indicated in the setting of emergency surgery, unless laboratory results have demonstrated the absence of significant anticoagulation [68].

Antiplatelet drugs

The effect of drugs that irreversibly inhibit platelet function will only wear off by replenishment with newly formed platelets. This occurs at a rate of 10–15% per day, and full restoration of normal levels therefore takes 7–10 days [69]. Drugs in this category include aspirin, clopidogrel, prasugrel and ticlopedine.

There are only two randomised controlled trials assessing a primary outcome of bleeding and thrombotic risk of continuing aspirin. The first had a composite outcome of major thrombotic and bleeding events within 30 days of surgery and there was no difference between aspirin or placebo [70]. Another RCT assessed this in patients at high cardiovascular risk undergoing non-cardiac surgery and found a significant reduction in major cardiovascular events on aspirin (1.2% vs 9.0%, $p = 0.02$), but was underpowered to detect any differences in bleeding rates [71]. The PEP trial showed a major bleeding rate of 2.9% in patients on aspirin vs 2.4% for patients on placebo ($p = 0.04$) [72] and a large meta-analysis found a 1.5-fold increased bleeding rate for aspirin, but without increased severity of bleeding except in intracranial surgery and possibly transurethral prostatectomy [73]. Two meta-analyses of aspirin in cardiac surgery found increased bleeding [74, 75], but this may be offset by a reduction cardiovascular events and overall mortality [76–78].

Overall, aspirin should be continued for most procedures except in patients at low risk for cardiovascular events having major surgery and those having high-risk procedures such as intracranial surgery.

There is very little information on the bleeding risk for clopidogrel monotherapy in general surgery. Although this appears to be higher than for aspirin [79–81], some expert groups suggest continuing the agent in a similar manner to aspirin [82]. The bleeding risk on dual antiplatelet treatment is increased [80, 81] and although neuraxial anaesthesia can be performed in patients on aspirin, it is contra-indicated in patients on clopidogrel, prasugrel and ticagrelor [68].

Non-cardiac surgery in patients with coronary stents

Surgery in patients with coronary stents in situ is a particular problem. The risk of major adverse cardiovascular events and stent thrombosis is highest in the first year after implantation, before endothelialisation is complete, which is 4–6 weeks for bare metal stents and 6–12 months for drug-eluting stents [83], and is associated with a mortality of up to 45% [84]. Perioperative death and ischaemic cardiac events were found in 42% of patients requiring surgery within

42 days of stent implantation vs 13% in those requiring surgery after this time ($p < 0.001$) [85]. In addition, the mortality was fourfold higher for surgery between 6 weeks and 1 year compared with surgery a year or more after stent implantation, independent of stent type [85]. The main determinant for ischaemic complications is early withdrawal of antiplatelet agents (hazard ratio 89.8), and is highest for those who stopped antiplatelet agents < 30 days after stent implantation [86]. Patients stopping clopidogrel within the first month of stent implantation had a 10-fold higher risk of death (7.5% vs 0.7%, $p < 0.0001$) in the following 11 months compared with those who continued it [87]. Overall, the short-term risk of stent thrombosis is reduced if only the thienopyridine (usually clopidogrel) is stopped, with a median time to stent thrombosis (stent implantation > 30 days previously) of 122 days vs 7 days if both were stopped ($p < 0.0001$) [88]. For a detailed discussion on the mechanisms of major adverse cardiovascular events and stent thrombosis, the role of antiplatelet agents in preventing these, and peri-operative management, we refer the reader to a review by Chassot et al. [89].

Overall, elective surgery should be postponed for a minimum of 4–6 weeks after bare metal stent implantation (preferably 3 months) and 6 months after drug-eluting stent implantation (preferably 12 months), after which point surgery should proceed while aspirin is continued [82]. For urgent procedures within this time frame, dual antiplatelet therapy should be continued, if at all possible [82]. Discontinuation of aspirin should only be considered in closed space surgery such as intracranial surgery, spinal canal and posterior eye chamber surgery [89]. Another option for patients on dual antiplatelet therapy requiring urgent surgery would be the use of specifically timed platelet concentrates. Thiele et al. suggest giving the last dose of aspirin and clopidogrel 12–24 h before a procedure, two pools of platelet concentrate 1–2 h before the procedure, restarting aspirin 6 h postoperatively and clopidogrel 24–48 h postoperatively depending on bleeding complications [90]. The pre-operative timing of the last dose of antiplatelet agents and subsequent platelet transfusion is based on the half-life of aspirin and clopidogrel and their active metabolites, and is not valid for prasugrel and ticagrelor.

Conclusions

In this paper, we have reviewed the peri-operative management of patients taking antithrombotic drugs. This is a contentious area and the absence of randomised controlled trials leads to significant variation in practice between hospitals, countries and the guidelines themselves. In a recent Canadian questionnaire, 20% of clinicians would not bridge, 40% would use prophylactic doses of low molecular heparin, and 40% would bridge with therapeutic doses of low molecular weight heparin in the hypothetical peri-operative management of a 70-year-old patient requiring a laparoscopic cholecystectomy who was taking warfarin for recurrent VTE [91]. Similar variety of opinion was demonstrated in the management of a 70-year-old man taking rivaroxaban for recurrent VTE requiring a total knee replacement; 62% gave the last dose 48 h, and 12%, 24 h, or 72 h, pre-operatively. Full dose rivaroxaban was restarted on day 1 in 20%, on day 2 in 25% and on discharge in 20%. Prophylactic low molecular weight heparin was chosen by 16%, therapeutic low molecular weight heparin bridging in 14% postoperatively and prophylactic rivaroxaban was also prescribed at various time points [91]. Equal variations in stopping and starting non-vitamin K antagonist oral anticoagulant drugs and the use of bridging were shown in the Dresden registry [50]. Given the growing concern regarding haemorrhagic complications associated with bridging, it is our opinion that bridging should only be considered in those at highest risk of thrombosis. Equally, full postoperative anticoagulation with non-vitamin K antagonist oral anticoagulant drugs should only be started when there are no concerns related to bleeding following a clinical review and not before 48 h following major surgery. Interestingly, while there is clear concern about thrombotic complications in patients on oral anticoagulation, the reverse may be true for those requiring antiplatelet agents, especially in those patients with coronary stents, as there continues to be a practice of interrupting antiplatelet agents in this group. A recent systematic review of 11 guidelines showed significant variation on when, and in which patient group, antiplatelet agents should be stopped [10]. Overall, given the poor prognosis of stent thrombosis, antiplatelet agents should not be stopped within

6 weeks to 3 months of bare metal stent and 6–12 months of drug-eluting stent implantation and only after multidisciplinary discussion related to the time after stent implantation, the necessity of surgery and the type of surgery.

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Competing interests

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Review Article

The current place of tranexamic acid in the management of bleeding

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Summary

There has been an explosion of interest in the ability of tranexamic acid to reduce morbidity and mortality in surgical and traumatic bleeding. Tranexamic acid has been shown to reduce mortality due to traumatic bleeding by a third, without apparent safety issues. It is now clearly established that intravenous tranexamic acid reduces blood loss in patients with surgical bleeding and the need for transfusion. It can also be used topically to reduce bleeding. Its use is being explored further in large pragmatic trials in traumatic head injury, postpartum haemorrhage and in upper gastro-intestinal haemorrhage. There are few side effects from the use of tranexamic acid except when administered in high dose where neurological events have been noted, possibly relating to tranexamic acid interfering with cerebral GABA and glycine receptors. However, clinical studies suggest that there is no increased efficacy in using a higher dose, and that a dose of 1 g intravenously in an adult patient has maximal efficacy, which is not increased by higher doses. The CRASH-2 trauma trial clearly showed no increase in thrombotic events after its use in trauma, indeed there was a significant reduction in myocardial infarction. However, trials of tranexamic acid in surgery have failed to adequately study its effects on the risk of postoperative venous and possible reduction in arterial thromboembolism, and this needs to be the subject of future research.

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Introduction

In the last decade, there has been an explosion of interest in the utility of tranexamic acid (TA) in reducing bleeding, fuelled, in particular, by the publication of CRASH-2 [1], the largest trauma trial ever conducted. This has also stimulated interest in the role of fibrinolysis in bleeding. This article presents an overview of our current understanding as to where TA may have clinical benefit, the appropriate dose and possible side effects.

Pharmacology of TA

Tranexamic acid (trans-4-(aminomethyl) cyclohexanecarboxylic acid) is a synthetic derivative of the amino acid lysine that competitively inhibits the activation of plasminogen to the serine protease, plasmin, via binding to kringle domains. Tranexamic acid is also a competitive inhibitor of tissue plasminogen activator. It blocks the lysine-binding sites of plasminogen, resulting in inhibition of plasminogen activation and fibrin binding to plasminogen and therefore impairment of fibrinolysis [2].

Tranexamic acid can also directly inhibit plasmin activity, but higher doses are required to reduce plasmin formation. Tranexamic acid is about ten times more potent in vitro than aminocaproic acid, and binds more strongly than aminocaproic acid to both the strong and weak receptor sites of the plasminogen

molecule in a ratio corresponding to the difference in potency between the compounds. Tranexamic acid is distributed throughout all body tissues and the plasma half-life is 120 min.

The efficacy of TA in reducing traumatic bleeding

The largest trial to date of antifibrinolytics: the Clinical Randomisation of Antifibrinolytics in Significant Haemorrhage (CRASH-2) trial, assessed the effects of early administration of TA in trauma patients with, or at risk of, substantial bleeding [1]. A total of 20 211 trauma patients from 40 countries were randomly assigned within 8 h of injury to either TA (1 g load, then 1 g over 8 h) or placebo. The primary outcome was in-hospital mortality within 4 weeks of injury. All-cause mortality was significantly reduced with TA (14.5% vs 16%; relative risk (RR) 0.91, 95% CI 0.85–0.97; $p = 0.0035$). The data from CRASH-2 showed that, following the second day, bleeding is not the main cause of mortality, and was ascribed to head injury, multi-organ failure and vaso-occlusive complications, all of which were reduced, although all except myocardial infarction were non-significantly reduced in those receiving TA. However, the critical question was whether there was a reduction in bleeding deaths, and indeed, a significant reduction in death due to bleeding by one-third was seen. The excitement about the application of the findings of CRASH-2 is that death due to traumatic bleeding is a global problem, and if TA was given to all those with, or at risk of, traumatic bleeding, this would result in a worldwide reduction in the number of deaths of 120 000 per annum. The response in the UK has been positive, with NHS England ensuring that all ambulances and paramedics carry TA; moreover TA needs to be administered in patients 'receiving blood products within 3 h of injury' under the Major Trauma Best Practice Tariff [3].

Despite the reduction in mortality due to bleeding, TA did not reduce transfusion requirements. Why might this be? The management of blood loss during trauma is not fine-tuned to compensate for losses as it is in surgical practice; blood is given empirically and blood losses not accurately measured. Also, investigators were asked to use their normal practice and the availability of blood components is variable between the 40 countries involved in the study – it is widely recognised that blood transfusion practice varies widely. We also hypothesised that a proportion of the reduction in deaths was not due to reduced bleeding but other mechanisms, perhaps due to the anti-inflammatory and/or anti-thrombotic effects of TA [4].

Timing of TA administration is important. Further analysis of CRASH-2 showed that treatment given in the first 3 h reduced the risk of death due to bleeding, with RR reduction in the first hour of 0.68 (95% CI 0.57–0.82; $p < 0.0001$) and 0.79 (95% CI 0.64–0.97; $p = 0.03$) between 1 and 3 h. However, treatment given after 3 h seemed to increase death due to bleeding, with a RR of 1.44 (95% CI 1.12–1.84; $p = 0.004$) [5]. Thus, TA should be given as early as possible to bleeding trauma patients. For trauma patients admitted late after injury, TA is less effective, and could be harmful.

Efficacy of TA in reducing surgical bleeding

Since the withdrawal of aprotinin, TA has been widely used to reduce bleeding in cardiac surgery, but it is now also used in other types of surgery. In 2007, a systematic review of randomly assigned trials assessing TA in elective surgery identified 53 studies that included 3836 patients [6]. Tranexamic acid reduced the need for blood transfusion by a third (RR 0.61, 95% CI 0.54–0.70). A further systematic review in 2012 [7], reflecting the increased interest in TA over the intervening years, identified 129 trials that included 10 488 patients, carried out between 1972 and 2011. In this meta-analysis, TA reduced the probability of receiving a blood transfusion by a third (RR 0.62, 95% CI 0.58–0.65; $p < 0.001$). This effect remained when the analysis was restricted to trials using adequate allocation concealment (RR 0.68, CI 0.62–0.74; $p < 0.001$). Fewer deaths occurred in the TA group (RR 0.61, CI 0.38–0.98; $p = 0.04$), although when the analysis was restricted to trials using adequate concealment there was considerable uncertainty (RR 0.67, CI 0.33–1.34; $p = 0.25$). The authors concluded that cumulative meta-analysis showed reliable evidence that TA reduces the need for transfusion.

Another systematic review of 104 randomly assigned trials examined whether the effect of TA on blood loss varies with the extent of surgical bleeding. The results suggest that, despite variation in the magnitude of blood loss between procedures and the heterogeneity of the studies included, the use of TA was associated with an overall reduction in surgical bleeding by about a third. This reduction in bleeding with TA is almost identical to the reduction in the risk of receiving a blood transfusion with TA suggesting, as expected in the closely monitored environment of an operating theatre, that unlike traumatic bleeding in CRASH-2, blood transfusion use was closely titrated to blood loss [8].

Efficacy of TA in postpartum haemorrhage

A Cochrane review in 2010 [9] concluded that TA decreased postpartum blood loss after vaginal delivery and caesarean section, but since there were only two randomised controlled trials, which were small and of unclear quality, further studies were needed to establish efficacy and safety. In a subsequent study Xu et al. [10] conducted a randomly assigned, double-blind, case–control study of TA 10 $ml.kg^{-1}$ vs placebo in 174 primiparous patients undergoing caesarean section (CS). Blood loss up to 2 h postpartum was significantly lower ($p < 0.01$) in the TA group (mean (SD) 46.6 (42.7) ml) than in the control group (84.7 (80.2) ml), but the blood loss in the period from placental delivery to the end of CS did not differ between the TA and control groups ($p = 0.17$). No significant abnormal vital signs were observed after TA administration. Ducloy et al. [11] studied the use of high-dose TA in a randomly assigned, controlled, multicentre, open-label trial. Women with postpartum haemorrhage (PPH) > 800 ml following vaginal delivery were randomly assigned to receive TA (loading dose 4 g over 1 h, then infusion of 1 $g.h^{-1}$ over 6 h) or not. Blood loss between enrolment and 6 h later was significantly lower in the TA group (median (IQR) 173 (59–377) ml) than in controls (221 (105–564) ml), $p = 0.041$. In the TA group, bleeding duration was shorter and progression to severe PPH was less frequent than in controls ($p < 0.03$). Red cell transfusion was needed in 93% of women in the TA group vs 79% of controls ($p = 0.016$). This study is the first to demonstrate that high-dose TA can reduce blood loss and maternal morbidity in women with PPH. However this and previous studies were not adequately powered to address safety issues, notably the rate of venous thrombo-embolism (VTE) postpartum. Postpartum women are at high risk of VTE, it remains one of the major causes of maternal mortality, and there is concern that using an antifibrinolytic drug may increase this risk.

The WOMAN study [12], is a large, pragmatic, randomly assigned, double-blind, placebo-controlled trial designed to determine the effect of early administration of TXA on mortality, hysterectomy and other morbidities (surgical interventions, blood transfusion, risk of non-fatal vascular events) in women with clinically diagnosed PPH. The use of health services and safety, especially thrombo-embolic effect will be assessed. Treatment entails a dose of TA (1 g by intravenous injection) or placebo (sodium chloride 0.9%) given as soon as possible after randomisation. A second dose may be given after 30 min if bleeding continues, or if it stops and restarts within 24 h after the first dose. The main analyses will be on an 'intention to treat' basis, irrespective of whether the allocated treatment was received or not. The study aims to recruit 20 000 women (and has recruited over 14 000 at time of writing), and will have over 90% power to detect a 25% reduction from 4% to 3% in the primary endpoint of mortality or hysterectomy; it is due to report in 2016/7.

Topical use of TA

There is reliable evidence that topical application of TA reduces bleeding and blood transfusion in surgical patients; however, the effect on the risk of thrombo-embolic events is uncertain [13]. Furthermore, high-quality trials are warranted to resolve these uncertainties before topical TA can be recommended for routine use.

Other areas where TA is being trialled

There are inadequate studies to ascertain whether TA will be beneficial in reducing gastro-intestinal (GI) bleeding and mortality, and it is debatable whether the results of CRASH-2 should be extrapolated from

trauma to GI bleeding. Thus, an ongoing trial is addressing this research question. The haemorrhage alleviation with TA – intestinal symptoms (HALT-IT) is currently randomising 8000 patients with acute upper GI haemorrhage to TA vs placebo [14]. The CRASH-3 trial is an international, multicentre, pragmatic, randomly assigned, double-blind, placebo-controlled trial to quantify the effects of the early administration of TA on death and disability in patients with traumatic brain injury. Ten thousand adult patients will be randomly assigned to receive TA or placebo. Treatment will entail a 1 g loading dose followed by a 1 g maintenance dose over 8 h [15].

Dose of TA

The original studies by Horrow et al. showed that, in cardiac surgery, a dose of TA of 10 $mg.kg^{-1}$ followed by 1 $mg.kg^{-1}.h^{-1}$ decreased bleeding during cardiac surgery and larger doses did not produce haemostatic benefit [16, 17]. CRASH-2 used this information to produce an empirical dose to provide adequate plasma levels to have an antiplasmin effect in adults. The meta-analysis by Ker et al. [8] also suggested that a dose of 1 g produced a reduction in bleeding that was not improved by giving higher doses. This study showed that a total dose of 1 g was likely to be sufficient for most adults and there was no evidence to support higher doses.

Since 2010, there have been a number of articles describing seizures with high-dose TA; using doses much greater than the original Horrow recommendations [17, 18]. In an elegant set of studies, Lecker et al. [19] showed there is structural similarity between the TA and inhibitory neurotransmitter-gated Cl^{-} channel glycine receptors, and demonstrated that TA inhibits glycine receptors and binds competitively to GABA type-A receptors. They proposed that the higher rate of TA-related seizures seen in cardiac surgery may relate to disruption of the blood brain barrier by cerebral emboli. However, it may also be that cardiac surgery is one of the few areas where very high doses of TA have been used. Anaesthetic agents with glycine receptor agonist properties such as isoflurane or propofol may be uniquely suited to prevent such seizures after surgery; although ultimately limiting the dose of TA to the original dose suggested Horrow appears as safe and efficacious as a higher dose.

Thrombotic risk

CRASH-2 showed that TA significantly reduced the risk of myocardial infarction, and had no effect on the rate of venous thrombo-embolism, reassuring physicians that it is safe to use in a trauma setting. Although there is strong evidence that TA reduces blood transfusion in surgery, there is still uncertainty as to whether TA may be associated with an increased risk of arterial and venous thrombo-embolism, and this uncertainty limits its widespread use. In a large meta-analysis [7], the effect of TA on myocardial infarction (0.68, CI 0.43–1.09; $p = 0.11$), stroke (1.14, CI 0.65–2.00; $p = 0.65$), deep vein thrombosis (0.86, CI 0.53–1.39; $p = 0.54$), and pulmonary embolism (0.61, CI 0.25–1.47; $p = 0.27$) was uncertain. A newly published analysis of the use of TA in hip and knee replacement in the USA has suggested that there is no increased risk of vascular occlusive events in this group of patients [20].

The effect of TA on thrombo-embolic events and mortality requires further attention. The ongoing Aspirin and Tranexamic Acid for Coronary Artery Surgery trial [21] should help resolve uncertainties around cardiac surgery, but there is still a need for a large pragmatic trial in other surgical patients. Furthermore, there is an exciting suggestion from CRASH-2 that the use of TA could reduce death due to postoperative myocardial infarction [22], making TA a highly cost-effective way of improving surgical safety. It is timely to resolve this uncertainty in an adequately powered randomly controlled trial.

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Competing interests

No other conflicts of interest.

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