Trauma Surgery 2

Haemorrhage control in severely injured patients

Russell L Gruen, Karim Brohi, Martin Schreiber, Zsolt J Balogh, Veronica Pitt, Mayur Narayan, Ronald V Maier

Most surgeons have adopted damage control surgery for severely injured patients, in which the initial operation is abbreviated after control of bleeding and contamination to allow ongoing resuscitation in the intensive-care unit. Developments in early resuscitation that emphasise rapid control of bleeding, restrictive volume replacement, and prevention or early management of coagulopathy are making definitive surgery during the first operation possible for many patients. Improved topical haemostatic agents and interventional radiology are becoming increasingly useful adjuncts to surgical control of bleeding. Better understanding of trauma-induced coagulopathy is paving the way for the replacement of blind, unguided protocols for blood component therapy with systemic treatments targeting specific deficiencies in coagulation. Similarly, treatments targeting dysregulated inflammatory responses to severe injury are under investigation. As point-of-care diagnostics become more suited to emergency environments, timely targeted intervention for haemorrhage control will result in better patient outcomes and reduced demand for blood products. Our Series paper describes how our understanding of the roles of the microcirculation, inflammation, and coagulation has shaped new and emerging treatment strategies.

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This is the second in a Series of three papers about trauma surgery

National Trauma Research Institute, The Alfred Hospital, Monash University, Melbourne, VIC, Australia (Prof R L Gruen MD, V Pitt PhD); **Centre for Neuroscience and Trauma, Barts and the London School of Medicine and Dentistry, Trauma Clinical Academic Unit, Royal London Hospital, London, UK** (Prof K Brohi MD); **Department of Surgery, Oregon Health and Science University, Portland, OR, USA** (Prof M Schreiber MD); **Department of Trauma, John Hunter Hospital, University of Newcastle, Newcastle, NSW, Australia** (Prof Z J Balogh MD); **Center for Injury Prevention and Policy, R Adams Cowley Shock Trauma Center, University of Maryland School of Medicine, Baltimore, MD, USA** (M Narayan MD); **and Department of Surgery, Harborview Medical Center, University of Washington, Seattle, WA, USA** (Prof R V Maier MD)

Correspondence to:
Prof Russell L Gruen, National Trauma Research Institute, 89 Commercial Road, Melbourne, VIC 3004, Australia
r.gruen@alfred.org.au

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Introduction

Exsanguinating haemorrhage is the most common preventable cause of death after trauma.[1] It causes approximately a third of the almost six million trauma deaths per year. About half occur before the patient reaches the hospital. All civilian and military trauma systems face the challenge of ensuring that bleeding patients receive timely and effective haemorrhage control.

Key messages

- Contemporary approaches to haemorrhage control combine early control of bleeding, management of coagulopathy, maintenance of critical perfusion, and management of the inflammatory response
- Early haemorrhage control minimises genomic activation and the harmful inflammation and coagulopathy caused by shock and resuscitation
- Topical haemostatic agents and interventional radiology are useful adjuncts to surgical control of bleeding
- Several pathogenic mechanisms contribute to trauma-induced coagulopathy, and the predominant mechanism changes during the clinical course
- Blind unguided protocols for blood component therapy in haemorrhagic shock and coagulopathy have safety and logistic concerns and trials of their effectiveness are underway
- Systemic treatments for coagulopathy might reduce the reliance on and demand for blood products
- Broad-acting drugs, such as tranexamic acid, that potentially affect inflammation, coagulation, and fibrinolysis, could modify responses to shock and improve outcomes
- In the future, treatments for haemorrhagic shock will be tailored to an individual's response by use of point-of-care tests and targeted therapies

Treatment approaches to haemorrhagic shock have transformed during the past two decades. From the Vietnam War until the 1990s, patients in shock received aggressive volume resuscitation with crystalloid solutions. More recent practices emphasise early administration of blood component therapies and tolerance of moderate hypotension until bleeding is controlled. These developments, which were consolidated in the Iraq and Afghanistan wars, are affecting the role of surgery in trauma patients. Previously, inability to prevent physiological exhaustion in exsanguinating patients meant that the primary focus in the operating theatre was damage control—ie, abbreviated initial surgery followed by ongoing resuscitation in the intensive-care unit. However, improvements in early bleeding cessation and haemostatic

Search strategy and selection criteria

We searched Medline, Evidence-Based Medicine Reviews, Cochrane Central Register of Controlled Trials, and Embase with the core terms "hemorrhagic shock", " wounds and injuries", "blast injuries", "fluid resuscitation", and "trauma" and the keywords "damage control", "fluid therapy", "hemostatic agents", "permissive hypotension", "blood component", "transfusion", and "angioembolisation". The appendix includes a full list of search terms. We restricted our searches of these databases to studies published in English between Jan 1, 2006, and Nov 28, 2011. We examined reference lists of relevant publications and reviews to identify further reports. 18 569 citations were screened and 501 relevant full text articles were reviewed, including 216 reviews. We preferentially cited systematic reviews rather than individual trials throughout the paper. On May 31, 2012, we updated the searches of all Cochrane systematic reviews addressing fluid resuscitation in injured patients to identify recent trials for inclusion in the meta-analyses presented in figure 2.

component resuscitation resulting in less physiological disturbance mean that completion of definitive treatment is often possible in the first operation.[2]

Much of our understanding of haemorrhage control is based on observational studies and preclinical research, which have characterised the physiological derangements of the shock state and the effects of treatment. This piecemeal collection of evidence supports contemporary approaches that aim to minimise dysregulated immune responses and harmful systemic effects of resuscitation.

Our Series paper describes how our knowledge of the microcirculation, inflammation, and coagulation has shaped new and emerging treatment strategies (table 1).

Microcirculation in haemorrhagic shock

Intravital microscopy has enabled better understanding of the crucial role that the microcirculation plays in mediation of the response to haemorrhagic shock and the inadequacy of fluid resuscitation as the only treatment.[3] Haemorrhage and resuscitation induce cellular changes that are characteristic of ischaemia–reperfusion injury—eg, production of reactive oxygen species, activation of inflammation, and apoptotic cell death (figure 1).[4]

The immunoinflammatory response comprises both innate and adaptive immunity. In severe shock, a large range of inflammatory mediators, cytokines, and oxidants are almost instantaneously produced and released in large quantities. This dysfunctional and exaggerated response is the presumed cause of the secondary organ damage associated with multiple organ failure and death. Further harm is caused by prolonged suppression of adaptive immunity, leading to increased risk of nosocomial infection.

Suppression of adaptive immunity was presumed to follow the proinflammatory burst as a consequence of the patient's endogenous attempt to control this burst;[5] however, this presumption has been proven incorrect.[6] The response to critical injury is associated with a so-called genomic storm, with substantially altered expression of as much as 75% of the entire human genome; changes to innate and adaptive immunity occur simultaneously.[7] The increase in genomic activity probably starts within minutes and is greatly increased within 6 h. The difference between complicated and uncomplicated recovery is defined by the patient's inability to achieve homoeostasis. Patients with uncomplicated recovery restore their genomic expression pattern to baseline within 2–3 days, whereas patterns remain altered and dysfunctional in those who develop complications.[8] Minimisation of the severity and duration of the dysfunctional microcirculatory response in the first minutes and hours after injury might prevent complications. Early control of bleeding and haemostatic resuscitation, incorporating correction of coagulopathy and minimal volume replacement, are likely to improve outcomes at least in part by facilitating recovery in the microcirculation.[4]

Early control of bleeding

In actively bleeding patients, prompt arrest of pronounced haemorrhage is the most important intervention to prevent death and reduce the harmful consequences of inflammation and resuscitation. Immediate compression of external wounds by a first responder or paramedic can substantially reduce volume loss. Limb tourniquets can control haemorrhage without high rates of adverse limb outcomes in patients with combat-related injuries,[9,10] and new devices have been designed that can effectively apply direct pressure to difficult sites such as the groin.[11] Early immobilisation of long-bone fractures and circumferential compression of pelvic fractures can also reduce blood loss.[12]

Although surgical techniques and operative exposures for rapid control of bleeding have changed little in recent years, an increasing number of adjunctive agents and techniques intended to improve surgical effectiveness have become available. A range of topical haemostatic agents are available for the field and operating theatre (table 2).[13] The ideal product would be fast-acting, non-antigenic, easily applied and removed, inexpensive, stable, and transportable, and would cause few side-effects.

The results of a systematic review[14] of six clinical studies and 37 preclinical animal trials showed that newer mucoadhesive agents and factor concentrators are better than older agents in the management of arterial and venous bleeding. Liquid and aerosol fibrin sealants are often used in elective and emergency surgery, and the results of a meta-analysis[15] of 18 trials (1406 patients) showed their use led to reduced blood loss and need for transfusions

	Past	Current strategies	Future directions
Bleeding	Aggressive definitive surgical control	Abbreviated initial surgery (damage control); planned definitive surgery after resuscitation complete; angioembolisation done separately; topical haemostatic agents	Prehospital interventions for control of bleeding; early surgery to stop bleeding and provide definitive procedures; seamless integration with interventional radiology; improved topical haemostatic agents
Coagulopathy	No or delayed management (after several transfusions of red blood cells)	Blind protocol-driven administration of factors (begun early)	Products tailored to patient's needs; guided by next-generation point-of-care tests; treatment begun early (possibly before hospital admission)
Perfusion	Aggressive volume resuscitation with crystalloid solutions	Haemostatic resuscitation with blood components; restrictive fluid resuscitation	Optimisation of fluid choice and minimal volume resuscitation strategies
Inflammation	No specific management	Minimal resuscitation with fluids that exacerbate inflammation	Targeting of aberrant host response with fluids, drugs, and other strategies; treatment begun early (possibly before hospital admission)

Table 1: Evolution of management of haemorrhagic shock

compared with controls. Other modes of delivery, such as absorbable pads, have been designed for more effective delivery of procoagulant factors (eg, fibrinogen and thrombin) to the site of major bleeding. These have been trialled in elective surgery, but their safety and efficacy in coagulopathic trauma patients are unknown.

Angioembolisation and other endovascular techniques are increasingly used for rapid haemorrhage control. In major vascular injury, temporarily placed catheters for proximal balloon occlusion might allow time for surgical access, control, and vessel repair. Endoluminal stent grafts are an alternative to surgery, especially for the aorta

For the **Fibrin Pad trial** see http://clinicaltrials.gov/ct2/show/NCT00977925?term=NCT00977925&rank=1

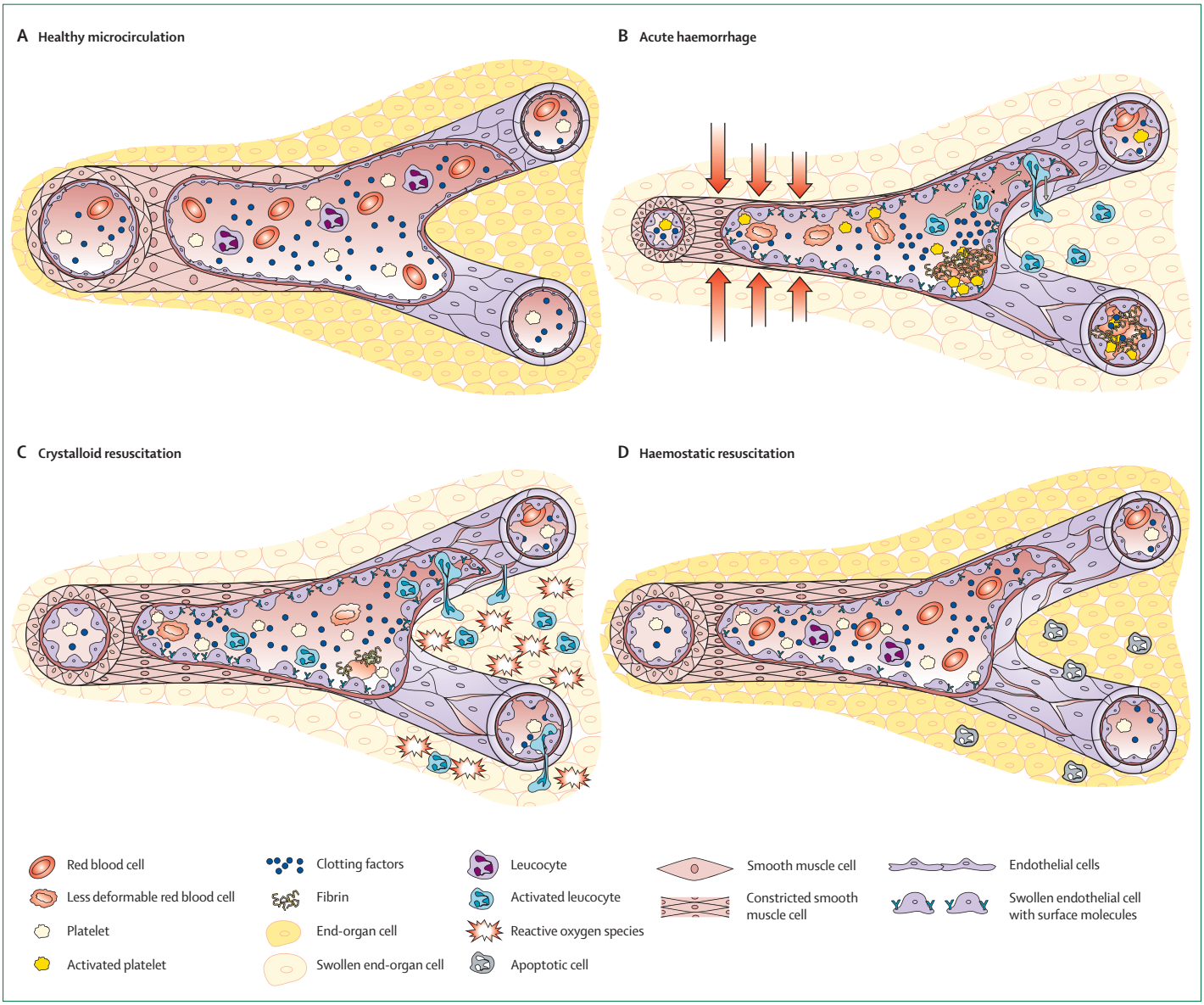

Figure 1: **Microcirculatory changes in haemorrhagic shock and resuscitation**
(A) In healthy capillaries, flow is facilitated by sufficient perfusion pressure and luminal diameter, fairly quiescent endothelial cell membranes, cellular deformability, an intact marginal acellular barrier, and balance between procoagulant and anticoagulant activity. (B) In acute haemorrhage, catecholamine-mediated arteriolar vasoconstriction causes capillary hypoperfusion and hypoxia, which in turn induce changes in membrane potential and ion distribution. Intracellular water content increases, resulting in capillary endothelial swelling and disruption of tight cell–cell junctions. Reduced perfusion pressure and endothelial swelling contribute to loss of capillary lumen, and obstruction by circulating cellular elements, debris, and activated platelets further impedes capillary flow. Erythrocyte deformability is decreased by hyperosmolarity, depletion of energy stores, and activation of the complement system, and can persist for hours after resuscitation. Trauma and inflammation induce surface expression of adhesion molecules on capillary endothelial cells, promoting rolling, adhesion, and eventual transmigration of activated leucocytes. Irreversible cellular and end-organ injury is caused by tissue hypoxia and anaerobic metabolism, leucocyte activation, and initiation of diffuse apoptosis. Critical hypoxia in arteriolar smooth muscle cells eventually causes intracellular acidosis, mitochondrial dysfunction, and ATP depletion, leading to diminished contractility and loss of vasomotor function, signalling progression to decompensated and then irreversible shock.[3] (C) In crystalloid resuscitation, clotting factors and other luminal components are diluted, and interstitial oedema and leucocyte–endothelial interactions are increased. Reperfusion can exacerbate inflammation and cause further injury through delivery of new activated leucocytes and generation of harmful free radicals and reactive oxygen species. (D) In haemostatic (or damage-control) resuscitation, blood loss, metabolic derangement, and fluid resuscitation are lessened, leading to less activation and disruption of the microcirculation, and less harm from reperfusion.[4]

	Mode of delivery (commercial examples)
Factor concentrators*	
Mineral zeolite	Granules (QuikClot); mesh bags (QuikClot Sport Advanced Clotting Sponge); gauze (QuikClot Combat Gauze)
Biological polymers	Powder (TraumaDex); nylon bags (self-expanding haemostatic polymer)
Mucoadhesives†	
Chitosan	Granules (TraumaStat); gauze (Chitogauze PRO, Celox, Hemogrip)
Chitin	Gauze (Modified Rapid Deployment Hemostat)
Mineral-based	Granules (WoundStat, WoundSeal Powder)
Synthetic peptides	Powder (InstaClot)
Polyethylene glycol	Gel (Coseal)
Oxidised cellulose	Gauze (BloodSTOP, Surgicel Fibrillar, Surgicel Nu-Knit)
Gelatin	Foam (Sugifoam, Gelfoam, Gelfilm)
Microfibrillar collagen	Powder (Avitene Flour, Helitene, Instat); rolled sheet (Avitene Sheets, EndoAvitene); sponge (Avitene Ultrafoam, Avitene Ultrawrap, Helistat); gel (Vitagel)
Procoagulant supplementors‡	
Human-derived factors§	Dry: oxidised cellulose and polyglactin matrix with thrombin and fibrinogen coating (Fibrin Pad); gauze imbedded with lyophilised fibrinogen and thrombin (Dry Fibrin Sealant Dressings); equine collagen patch with fibrinogen and thrombin (TachoSil) Liquid or aerosol: fibrin sealants (Tisseel, Evicel, Crosseal); gelatin–thrombin suspension (Floseal)
Bovine-derived factors¶	Gauze (FastAct); glue (BioGlue); sponge (TachoComb)
Plant-derived factors	Powder (HemoStase MPH, Arista)
Synthetic factors¶	Solution (Recothrom)

The appendix lists the manufacturers of all products. *Rapidly absorb water from blood to concentrate factors that promote clot formation. †Adhere to tissues and form a physical barrier to seal bleeding wounds. ‡Deliver procoagulant factors to bleeding wounds to promote clot formation. §Examples include fibrinogen, thrombin, calcium, and coagulation factor XIII. ¶Examples include thrombin.

Table 2: Topical haemostatic agents

and its major branches, and might be associated with less bleeding and tissue damage than is surgery.

Even in hypotensive patients, pelvic-fracture-associated arterial bleeding can be effectively treated with internal iliac artery embolisation or selective angioembolisation; gluteal necrosis occurs in approximately 5% of patients.[16,17] However a substantial proportion of pelvic haemorrhage arises from veins and fracture surfaces, and debate persists about whether the best primary intervention is pelvic arterial embolisation or extraperitoneal packing and external fixation with secondary angiography.[18] In the absence of substantial coagulopathy, most pelvic venous bleeding is self-limited when timely haemostatic resuscitation is provided.

In the acute management of bleeding liver injuries, the two main indications for angioembolisation are primary haemorrhage control in haemodynamically stable patients with CT evidence of active arterial bleeding and adjunctive haemorrhage control in patients with uncontrolled suspected arterial bleeding despite emergency laparotomy.[19] Hepatic necrosis is the main complication and occurs in approximately 10% of patients.

Patients exsanguinating from splenic injuries are usually treated with splenectomy. Angiographic techniques directed at the spleen are generally used as an adjunct to non-operative management, and a systematic review[20] of 33 studies (10 157 patients with blunt splenic injuries) showed that embolisation of the splenic artery was associated with lower operation rates and higher rates of splenic salvage than was observation alone in patients with high-grade injuries.[20]

Combined angiographic and surgical approaches could provide advantages for exsanguinating patients with multiple injuries and especially for management of major vascular, high-grade liver, or pelvic bleeding. A new generation of operating theatre is emerging—eg, resuscitation with angiography, percutaneous techniques, and operative repair (RAPTOR) suites, which incorporate advanced interventional radiology and resuscitation capabilities and minimise the need to move unstable patients between hospital departments.[21]

Management of coagulopathy

Trauma-induced coagulopathy

Coagulopathy usually accompanies severe haemorrhage in trauma patients. As many as 25% of severely injured trauma patients have an established coagulopathy when they arrive in the emergency department.[22] The incidence and severity of coagulopathy increase in hospital as bleeding continues and additional injuries are induced by infusions, transfusions, and surgical dissections. Coagulopathy is associated with early and late mortality[23,24] and increased incidence of subsequent acute lung injury, multiple organ failure, and infections, which consequently increase ventilator requirements and the length of stay in intensive-care units and hospital.[25]

Knowledge developments in the epidemiology, mechanisms, and consequences of coagulopathy in trauma have been central drivers for changes in management. Key factors include the description of trauma-induced coagulopathy and particularly identification of the early endogenous component of the disorder—ie, acute traumatic coagulopathy.[26] These developments have focused management of coagulopathy on the very earliest stages of care, even before the patient reaches the hospital. Elucidation of the underlying pathophysiology and discovery of new mechanisms for coagulopathy have provided a platform for a large domain of translational research in trauma.

Several pathological mechanisms contribute to trauma-induced coagulopathy. Different mechanisms occur with different patterns of injury and physiology, and the predominant mechanism changes at different times in the clinical course of the patient.[27] Acute traumatic coagulopathy is an early endogenous coagulopathy that is present in about one in four trauma patients and characterised by systemic anticoagulation and fibrinolysis.[28] It seems to be driven by severe shock in the presence of some degree of physical tissue trauma.[23] Although the underlying pathological process remains unclear, studies[29] suggest that the protein C system could have a central role.[30] Thus, acute traumatic coagulopathy seems to be a maladaptive response to overwhelming trauma. It is established within minutes of injury and

has been identified at the scene of the injury in prehospital research studies.[31] The presence of acute traumatic coagulopathy on arrival at hospital strongly correlates with early and late morbidity and mortality.[23]

Historically, loss or consumption of coagulation factors was thought to be the central mechanism for traumatic coagulopathy.[32] The degree and timecourse of reduction in procoagulant factor activity in trauma-induced coagulopathy remains unclear, but initially these factors do not fall to concentrations that would affect coagulation function.[33] Human and experimental models suggest that concentrations of fibrinogen are the first to fall, but usually these concentrations remain higher than those that would previously have provoked replacement, until substantial transfusions of red blood cells have been received.[34,35] Other procoagulant factors seem even less severely affected than fibrinogen.[33]

Dilution of clotting factors undoubtedly contributes to trauma-induced coagulopathy and possibly becomes the dominant cause during transfusion of red cells in all patients without other coagulation therapy support.[36] In some trauma systems, prehospital administration of substantial amounts of crystalloid or colloid solutions contributes substantially to the incidence of coagulopathy on arrival at hospital.[37] Even in the absence of crystalloid resuscitation, some amount of autoresuscitation in hypovolaemic states might contribute to the mild reductions in coagulation factors noted at this early stage.[34] Clear-fluid or red-cell transfusions are likely to rapidly exacerbate dilutional coagulopathy.[34]

Systemic hypothermia and acidaemia are classically thought to be central mechanisms of trauma-induced coagulopathy because of their inhibitory effects on procoagulant enzyme function. However, acidaemia seems only to affect protease function to an extent that could be clinically relevant when it is very severe (ie, blood pH <7·2).[38] Similarly, only severe hypothermia is associated with important functional decreases in protease activity,[39] although platelet aggregation and overall platelet function are reduced at temperatures lower than 35°C.[39] Hypothermia and acidaemia are probably markers of the severity of the underlying shock state and therefore markers of the endogenous coagulopathy that results from systemic hypoperfusion. In an experimental model of trauma-induced coagulopathy, correction of acidaemia alone did not restore normal coagulation.[40] Although severe acidaemia and hypothermia are thought to be important contributors to trauma-induced coagulopathy, their role now seems less central to pathogenesis.

Several other putative mechanisms that have yet to be clearly defined could contribute to trauma-induced coagulopathy, including inflammation, platelet dysfunction, and underlying genetic variations.[26] Because inflammatory and coagulation pathways are closely connected, coagulation is likely to be affected in some way by massive systemic activation of innate immunity in severe injury. Platelets are central components of immunity and coagulation, but little is known about their function or contribution to trauma-induced coagulopathy.[41] Platelet counts are well preserved initially in trauma, but preliminary evidence suggests substantial dysfunction in some trauma-induced coagulopathy states.[42] Underlying genetic variations in coagulation are known to exist in the general population but their effects on traumatic haemorrhage are not yet known. Finally, patients taking anticoagulants for premorbid disease are increasingly common; such drugs might exacerbate and complicate all mechanisms of trauma-induced coagulopathy.[43]

Blood component therapy

Blood component therapy in the form of plasma, platelets, and cryoprecipitate is the main treatment for trauma-induced coagulopathy. Recognition that coagulopathy occurs soon after injury has led to targeted haemostatic resuscitation strategies and massive transfusion protocols that promote early and aggressive treatment.[44]

Retrospective studies[45] have suggested that high-dose fresh frozen plasma and transfusions of red cells might be associated with improved survival compared with low-dose protocols, and clinical trials are imminent. Some transfusion protocols call for four-to-eight times more plasma transfusions than previously given. Although evidence from previous studies[45] is promising, these approaches raise concerns about the supply and potential adverse effects of plasma. The provision of large amounts of thawed plasma to trauma patients within minutes of hospital arrival is challenging and potentially wasteful.

For more on the **clinical trials** see http://www.clinicaltrials.gov/ct2/show/NCT01545232?term=PROPPR&rank=1

Freeze-dried and lyophilised plasma are logistically attractive options that are used in some military operations.[46] Lyophilised plasma is derived from dehydrated liquid plasma and stored as a powder at room temperature and can be rapidly reconstituted with water and used at any phase of care, including in prehospital settings. Its use ensures that transfusions in which the ratio of plasma to packed red blood cells is high are provided early to patients needing massive transfusion. Reconstituted lyophilised plasma maintains approximately 80% the factor activity of fresh liquid plasma and is better than thawed fresh frozen plasma.[47]

A high-dose approach has also been recommended for platelet transfusions and fibrinogen replacement therapy. This approach is supported by evidence from cohort studies, which suggest that survivors of trauma haemorrhage received higher doses of these products than did non-survivors.[34,48–50] These studies have several sources of bias and confounding, such as the relation between the speed and severity of haemorrhage and the logistic ability to provide these products rapidly.[51] Furthermore, the success of these high-dose plasma regimens could be at least partly because of the associated reduction in clear fluid use and subsequent reduction in iatrogenic dilutional coagulopathy.[52]

Several compelling reasons support a move away from blood component therapy for treatment of coagulopathy. The main concerns are the safety, demand, and logistics of supply. Little evidence exists to prove that blood component therapy can effectively correct coagulopathy in trauma. Standard treatment components, such as plasma, are still dilute in terms of clotting factors, and the transfusion of packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate in an equal ratio (1:1:1:1) produces a solution containing only half to two-thirds of the active elements in whole blood (haematocrit 29%, platelet count 87 000, coagulation activity 65%, and 750 mg fibrinogen).[53] To postulate how blood-derived products would fully reverse coagulopathy is difficult, although continuous supplementation could prevent exacerbation of an existing coagulopathy.[34]

Some of the components in plasma might be unnecessary for the treatment of trauma-induced coagulopathy, or at least for the treatment of specific mechanisms in a particular patient. Furthermore, some aspects of trauma-induced coagulopathy, such as fibrinolysis, are not treated by these compounds. These issues have prompted the search for new therapeutics that might be used as adjuncts or replacements for blood component therapy.

Systemic treatments

Fibrinogen concentrate has generated much interest as a targeted treatment in trauma-induced coagulopathy. Its use is common in Europe, where it is often given when thromboelastography shows evidence of reduced formation of fibrin networks.[54] However, the evidence is from case series only, and clinical trials are urgently needed to assess the roles of fibrinogen concentrate in replacement of lost fibrinogen substrate and as a potential treatment for many forms of trauma-induced coagulopathy.[55]

Procoagulant therapy has also been of interest. The results of clinical trials of recombinant factor VIIa in unselected patients who needed transfusion showed that factor VIIa had some effects on red-cell transfusion requirements but did not affect overall mortality; the largest trial so far was stopped early because of futility.[56,57] Unfortunately, these studies did not assess the effect of recombinant factor VIIa on the coagulation system. They were also done at a time when trauma-induced coagulopathy was thought mainly to be a failure of procoagulant function. Use of recombinant factor VIIa has decreased substantially since these trials[56,57] were published and damage control principles became popular. Whether some forms of coagulopathy exist that might respond optimally to recombinant factor VIIa remains unknown. Other procoagulants, in particular prothrombin complex concentrates, continue to be of interest. Prothrombin complex concentrates have a definite role in reversal of the effects of warfarin in trauma patients, but their safety and efficacy in trauma-induced coagulopathy has yet to be assessed in clinical trials.[58]

Mechanistic evidence suggests that fibrinolysis has a central role in acute traumatic coagulopathy, although overt hyperfibrinolysis is not often apparent with thromboelastography.[59] A large international clinical trial[60] of the antifibrinolytic tranexamic acid showed improved survival at 30 days compared with placebo in patients deemed at risk of bleeding, when the drug was given early in the clinical course.[60] Tranexamic acid has subsequently been incorporated into major haemorrhage protocols in many institutions and research into its efficacy and optimum use is ongoing.

Maintenance of critical perfusion

The third goal of haemorrhage control is to maintain adequate perfusion before, during, and after arrest of bleeding and thereby minimise further cellular and organ injury. Perfusion and inflammation are closely related; inflammation is a consequence of hypoxic tissue damage during low-flow states, over-resuscitation, and the generation of reactive oxygen species during reperfusion.

Restrictive fluid resuscitation is standard care in many trauma systems. Early aggressive resuscitation of haemorrhagic shock with predominately saline-based regimens is associated with increased bleeding due to displacement of established clots, cardiac dysfunction, abdominal compartment syndrome, harmful inflammation, acute respiratory distress syndrome, multiple organ failure, and increased mortality.[61] Key unresolved issues affecting fluid resuscitation include the degree and duration of hypotension and perfusion that can be tolerated, which fluid to use, and the optimum management of reperfusion once bleeding is controlled.

The US Committee on Tactical Combat Casualty Care and the UK military's Clinical Guidelines for Operations do not recommend fluid resuscitation in the field unless the patient has a diminished mental status or an absent radial pulse (equivalent to systolic pressure of approximately 90 mm Hg), in which case only small volume boluses are given until a palpable pulse returns.[62,63] The degree of arterial hypotension that can be tolerated is unclear, partly because capillary perfusion can vary by a factor of 100 in healthy patients, and, in the pathological state, arterial pressure correlates poorly with capillary perfusion. The results of observational studies[64,65] show that the use of vasopressors to support arterial pressure in hypovolaemic patients is associated with worse outcomes, probably through exacerbation of already diminished capillary perfusion.

Ischaemic stress is determined by the degree and duration of hypoperfusion. Although overresuscitation can exacerbate systemic inflammation, dilutional coagulopathy, and rebleeding, under-resuscitation is also harmful and can result in ischaemia-mediated inflammation and coagulopathy. A combination of both approaches might be ideal. Evidence from a randomised

trial[66] in a porcine model of haemorrhagic shock with and without blast injury showed that initial saline-based resuscitation to systolic pressures of 80 mm Hg for 60 min followed by resuscitation to 110 mm Hg led to attenuation of markers of acute traumatic coagulopathy and systemic inflammation, improved tissue perfusion, reduced metabolic acidosis, and prolonged survival compared with sustained hypotensive resuscitation. Whether a similar strategy will be effective in human beings is unknown.

Because of the tendency of isotonic crystalloids to exacerbate coagulopathy and inflammation, the search continues for safer and more effective fluids. The ideal initial resuscitation fluid should have oxygen-carrying capacity, promote capillary perfusion, and not exacerbate coagulopathy or inflammation. Hypertonic saline seems to improve tissue perfusion through restoration of circulating intravascular volume and attenuation of postinjury microcirculatory oedema.[67] It also seems to cause sustained attenuation of harmful inflammation in patients with shock by decreasing neutrophil activation, reducing serum concentrations of tumour necrosis factor, increasing concentrations of anti-inflammatory cytokines, and lessening the shock-induced norepinephrine surge.[68] Unfortunately these benefits have not translated to improved outcomes in clinical trials.[69–71] Based on our search and update of existing reviews,[69,72–74] we did a meta-analysis of all trials that compared types of fluids for resuscitation in haemorrhagic shock; no type of fluid was better than another in terms of mortality endpoints (figure 2).

In many centres, and some ambulance services, plasma or blood, or both, are used as the primary resuscitation fluids. Provision of blood before hospital arrival is logistically challenging. Various preparations, including frozen blood, have been developed. Storage lesion in packed red blood cells seems associated with increased morbidity and mortality, although the age of red cells at which these effects become clinically important is unclear because of the heterogeneity and limitations of completed studies.[75] A large multicentre trial of old versus new red-cell transfusions is underway in stable critical-care patients;[76] an equivalent trial is needed in major trauma resuscitation.

Fresh whole blood has been associated with improved survival compared with component therapy.[77] The potential benefits of transfusion with fresh blood over banked blood are partly because of greater red-cell deformability and subsequent restoration of functional capillary density closer to baseline levels. However, the use of fresh blood is limited by the inability to store it for more than a few days and the inherent risks of infectious diseases if comprehensive screening tests cannot be completed. Fresh whole blood is used mainly in military operating theatres when adequate blood components are not available to provide transfusions with high ratios of plasma to red blood cells, platelets are not available, or patients are not responding to damage control resuscitation.[78]

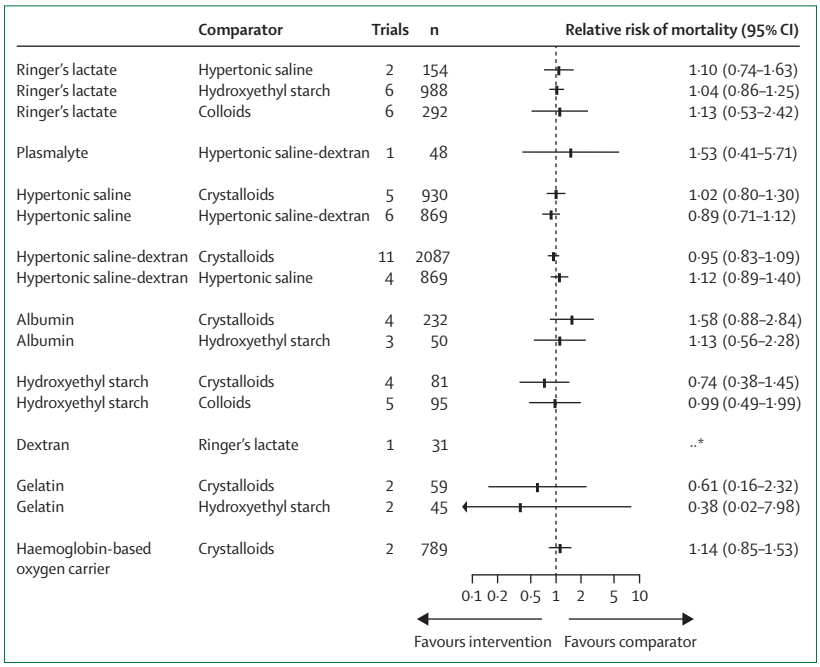

Figure 2: **Overview of human trials of resuscitation fluids in haemorrhagic shock, by intervention**
Trials involving trauma patients with acute haemorrhagic shock were pooled in a fixed-effects meta-analysis to establish relative risk and 95% CI. See appendix for forest plots and references. *Not estimable because raw data were not obtained. However, the trial reported no difference in mortality between groups receiving dextran or lactated Ringer's solution.

Management of the inflammatory response

Specific treatments to attenuate the inflammatory response to haemorrhagic shock are under investigation. They show the prevailing reductionist approach to the molecular basis of disease, and research has mainly focused on isolated components of the complex immunological processes. A wide range of mediators, including cytokines, cell-membrane lipids, enzymes, and oxidants, have all been implicated and, in most cases, have been investigated in well controlled murine models designed to mimic human disease. Unfortunately, most interventions focused on single components or limited pathways have not achieved any reproducible clinical benefits so far. Because of the extensive redundancy and parallel efficiencies of the immune system, only a multipronged approach or a sufficiently broadly effective treatment seems likely to have a measurable clinical benefit.

Several approaches merit further investigation. Replacement of rapidly depleted antioxidants in critically ill surgical patients decreases the risk of organ failure (especially adult respiratory distress syndrome), length of stay, and overall mortality.[79] Massive doses of vitamin C decrease microvascular leak and volume requirements after burn injuries,[80] and lyophilised plasma reconstituted with vitamin C and water is better than fresh frozen plasma for haemorrhage control, suppression of dysfunctional inflammation, and antioxidant capacity in complex multiple-injury porcine models.[81,82] Whether

generic antioxidants or specific combinations of agents are necessary is unclear.

By inhibiting the conversion of plasminogen to plasmin, tranexamic acid could modulate plasmin-mediated inflammation, neurotoxicity, and fibrinolysis.[83] The interaction between coagulation and several immune pathways makes plasmin an appealing target.[83] Other broad anti-inflammatory approaches also seem encouraging—eg, inhibitors of intracellular signalling pathways through candidates such as p38.[84] Similarly, to reverse the detrimental suppression of adaptive immunity, restoration of interferon-γ-dependent pathways with exogenous interferon seems appropriate to explore. Finally, therapeutic hypothermia is known to provide cellular protection and mitigate the harmful effects of ischaemia–reperfusion syndrome in cardiac surgery, but so far its use in trauma has been restricted to trials of limb ischaemia and traumatic brain injury.[85,86] A research agenda is planned that encompasses mechanistic studies and investigations into the effects of hypothermia alone or in combination with novel cytoprotective agents on coagulation, drug metabolism and effect, and clinical outcomes.[87]

Early and personalised interventions

Despite improved knowledge about the microcirculation, inflammation, and coagulation, treatment options are few and therapeutic targets are still poorly understood. In particular, treatment protocols do not factor in the coagulation state of patients or their likely response to transfusion. Diagnostic tests such as prothrombin and partial thromboplastin times are inaccurate, do not indicate coagulation functional status in trauma, and are not back in time to guide treatment during active haemorrhage and transfusion. Accurate and reliable point-of-care methods to predict, diagnose, and monitor bleeding patients and responses to treatment are needed. Such tests would allow rapid administration of products to patients who are most likely to benefit from them without the risk of exposing others to unnecessary risks.[88]

To enable early initiation of treatment, clinical prediction strategies that identify patients likely to benefit from massive transfusion in civilian and military settings[89,90] or those with acute traumatic coagulopathy[91] have been developed on the basis of injury mechanisms, vital signs, and findings after initial assessment. These strategies are reasonably accurate (area under receiving operating characteristic [AUROC] curve >0·8), have good negative predictive values, and have positive predictive values that represent acceptable over-triage rates for initiation of treatment.

The use of thromboelastography to guide early management of coagulation has received much attention. This method has proven accuracy for diagnosis of trauma-induced coagulopathy, potentially within 5 min of collection of a blood sample.[92] Thromboelastography is also better able to describe the functional defects in coagulopathy than are other techniques. For example, thromboelastography has shown that acute traumatic coagulopathy is mainly a problem of reduced clot strength rather than delayed initiation or propagation of clot formation.[92] However whether this technology can identify different underlying mechanisms of trauma-induced coagulopathy or effectively guide coagulation treatment during haemorrhage is unknown. These machines are also fragile and designed for elective laboratory environments, and although they are increasingly used in trauma patients, they are not ideally suited to the robust demands of emergency settings.

Future management of trauma-induced coagulopathy and the overall inflammatory response needs to move away from the blind, unguided replacement of blood products in patients who are bleeding. Based on our understanding of the microcirculation, inflammation, and coagulation in haemorrhagic shock, a therapeutic window probably exists, during which the stimuli of harmful inflammation can be controlled and the genomic response could be altered. Control of bleeding and minimisation of resuscitation helps remove the stimulus for inflammation. Early treatment with sufficiently broad agents followed by treatment tailored to an individual's biological response should then be the goal. The finding in the CRASH-2 trial[93] that tranexamic acid is efficacious when given within 3 h of injury but might be harmful when given later after injury emphasises the time-critical nature of some interventions.

Haemorrhage control should be prioritised in prehospital settings and upon arrival at hospital. Improved diagnostic devices are needed to characterise specific defects of trauma-induced coagulopathy and assess response to treatment. New treatments based on novel targets should reduce the dependence on allogeneic blood donation and complex logistic supply chains.[94]

As approaches to haemorrhage control evolve, some technologies and treatments that have been available since the 1950s—eg tranexamic acid, thromboelastography, and lyophilised plasma—are now being embraced. However, with the exception of tranexamic acid, little robust evidence exists for their usefulness, serving as a reminder that future strategies should be guided by large, robust clinical trials, which in turn need strong trauma research networks and thoughtful approaches to trauma trial design by researchers and regulatory authorities.

Contributors

RLG planned the review; led writing of the paper; coordinated evidence searches, interpretation of evidence, and illustrations; and drafted the abstract and sections about early control of bleeding, early targeted treatment, the introductory and concluding comments, and summary points. KB planned the review and drafted sections about coagulopathy and early targeted treatment. MS drafted sections about management of perfusion. ZJB drafted sections about microcirculatory changes and the figure. VP coordinated evidence searches, did the meta-analyses, interpreted the findings, and drafted the tables and supplementary materials. MN drafted the section about topical haemostatic agents. RVM drafted sections about inflammation and immunity. All authors revised and edited all sections of the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

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