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CRITICAL CARE

Haemostatic resuscitation

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Editor's key points

- Advances in the pathophysiology of shock and coagulation have led to changes in trauma resuscitation.
- These include reduced volume replacement/deliberate hypotension to reduce bleeding and aggressive coagulation management.
- Further studies are required to confirm improved outcomes resulting from these approaches.

Summary. Recommendations for resuscitation of patients in early haemorrhagic shock, with active ongoing bleeding, have evolved in recent years. This review covers current theories of the pathophysiology of shock and recommended treatments, including damage control surgery, deliberate hypotensive management, administration of antifibrinolytics, early support of the coagulation system, and the possible role of deep anaesthesia. Future directions for resuscitation research are discussed.

Keywords: resuscitation; transfusion; trauma

Haemostatic resuscitation describes the process of restoring and sustaining normal tissue perfusion to the patient presenting in uncontrolled haemorrhagic shock, with an emphasis on preservation of effective clotting. The concept incorporates elements of first aid, trauma surgery, and operative anaesthesia, and covers relevant medical care from the moment of injury forward until haemodynamic stability is achieved. It is team-based rather than speciality-based, and has been driven by hard-won experience and evidence-based scientific research in both civilian trauma centres and the crucibles of combat casualty care in Iraq and Afghanistan. Haemostatic resuscitation acknowledges the need to make clinical decisions in the face of uncertainty regarding the patient's prior medical condition, the anatomic source of bleeding, and the expected volume and duration of haemorrhage. It is based on emerging recognition of the way in which coagulopathy develops after injury, and on two decades of research—often highly controversial—into clinical techniques to improve survival. This manuscript will describe the pathophysiology of haemorrhagic shock and will trace the evolution of resuscitation science in recent years, concluding with a review of current controversies and areas of active research.

The pathophysiology of haemorrhagic shock

Figure 1 is a representation of the physiological impact of severe injury, illustrating that trauma is both a local and a systemic disease. Pathophysiology begins with direct damage to tissue by external energy (the definition of trauma). This creates both tissue injury and pain. Disruption of blood vessels and solid organ parenchyma causes haemorrhage and a decrease in cardiac output. Systemic compensation occurs through increased sympathetic outflow, leading to increased heart rate and vasoconstriction of non-essential tissues.[1] When bleeding is severe enough to overwhelm systemic compensation, the result is tissue hypoperfusion, or shock.

Damaged and under-perfused cells become distressed, and react through release of toxins and mediators.[2] Anaerobic metabolism generates metabolic by-products (lactate and other acids) that create further damage both locally and systemically. Hundreds of other compounds are released by the ischaemic cell, including interleukins, tumour necrosis factor, and complement proteins.[3] These bioactive molecules in turn create an amplified reaction throughout the body, transforming a local event into a systemic disease.

The full extent of factor release from injured and ischaemic cells is incompletely understood, in part because it varies from one cell type to another and across the spectrum of human genomic and proteonomic expression. Recent active research in this area, however, has revealed a key component of this response. Thrombin triggers liberation of protein C from thrombomodulin; protein C binds to plasminogen activator inhibitor-1, thus producing a fibrinolytic state.[4] Alternative explanations for the fibrinolytic state observed after major trauma have also been advanced.[5] While understandable in a teleological sense—most cellular ischaemia arises from thrombosis—this is a maladaptive response to traumatic haemorrhage. Discovery of this effect began with a clinical observation that severely injured trauma patients were coagulopathic even before significant blood loss or dilution with resuscitative fluids had occurred.[6 7] Further, those patients with altered coagulation function at the time of hospital admission had substantially worse outcomes than similar patients who were not coagulopathic (defined as an international normalized ratio >1.5), even with similar

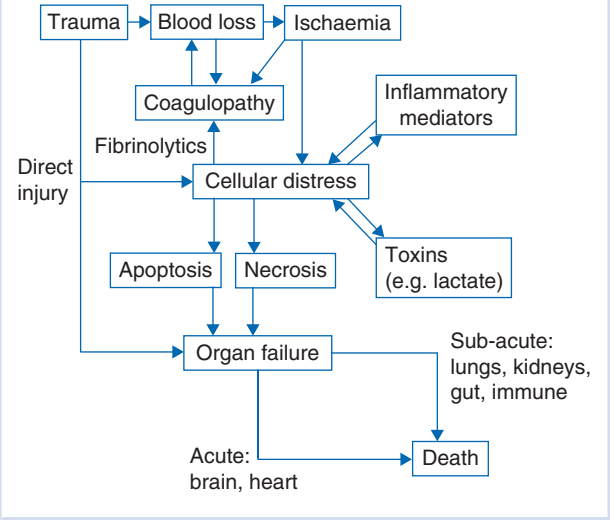

Fig 1 The pathophysiology of haemorrhagic shock.

degrees of injury (Fig. 2).[7 8] Whether this finding represents differences in blood loss at the time of admission or a genetic predisposition to mortality after trauma is unknown, but is an important question for future study.

In any case, coagulopathy leads to increased haemorrhage and thus progression of ischaemia, causing further cellular injury in a downward spiral that will lead to death from exsanguination if not interrupted. Consumption of available clotting factor and platelet reserves, serum acidosis, and systemic hypothermia will contribute to the 'bloody vicious cycle' of bleeding, coagulopathy, and further bleeding.[9] Medical care itself contributes an iatrogenic component to the pathophysiology of acute haemorrhage. Traditional thinking about resuscitation, based on animal models of controlled haemorrhage developed in the 1950s, emphasized the importance of fluid volume administration,[10] even though clinical data suggested that administering fluids during uncontrolled haemorrhage was associated with increased bleeding.[11] This is largely a mechanical phenomenon: increased fluid volume increases cardiac output through the Frank–Starling relationship, leading to increased arterial pressure. Increased pressure forces more fluid out of the damaged circulation, and 'washes away' early extra-vascular clots.[12] Other effects are more subtle. Asanguineous resuscitation fluids—isotonic crystalloids and non-blood colloids—dilute the concentration of red cells, clotting factors, and platelets.[12] Exogenous fluids are likely to be cooler than body temperature, contributing to hypothermia. Rapid administration of crystalloids damages the endothelial glycocalyx, leading to increased extravasation.[13] Research also suggests that crystalloids may have pro-inflammatory side-effects.[14]

Death from haemorrhagic shock occurs via one of the two common pathways. Acute exsanguination occurs early after injury and is largely the result of anatomically uncorrectable lesions. Death arises from failure of the cardiovascular system to maintain minimal cardiac output. Subacute death occurs when anatomic control is obtained—preserving cerebral and coronary perfusion short of acute failure—but the cumulative burden of ischaemia proves lethal.[15] This is the patient who survives initial surgery and resuscitation only to die days, weeks, or even months later as the result of multiple organ system failure. Acute lung injury is common after severe trauma, as the combined result of direct pulmonary injury, aspiration, massive transfusion, ischaemia, and systemic inflammation. Pulmonary failure may be followed by acute renal failure, gut dysfunction, and immune system compromise, leading to serial septic episodes and episodic haemodynamic instability until intensive care is no longer effective.

Goals of early resuscitation

Early resuscitation is defined as medical care provided from the moment of injury until definitive anatomic control of haemorrhage is achieved, typically through surgery or angiographic embolization.[16] Early resuscitation is characterized by uncertainty as to the source of bleeding, the quantity of blood lost, and the anticipated duration of haemorrhage. While the goal of resuscitation in general is to restore normal systemic oxygen delivery, during early resuscitation the advantage of reducing ischaemia must be weighed against the iatrogenic prolongation of haemorrhage which was outlined above.

During active haemorrhage, clinical goals have shifted from the traditional approach of rapid bolus fluid administration in an effort to normalize arterial pressure. A more nuanced approach is recommended, which attempts to preserve and support coagulation while providing the least cardiac output necessary to sustain vital organ function. Because the threshold of lethal (or organ specific) ischaemia is heterogeneous across the population, early resuscitation requires substantial clinical judgement and experience, and management recommendations are guidelines rather than definitive standards of care.

Table 1 shows the major components of haemostatic resuscitation and the approximate level of evidence in support of each recommendation. Each of these components is discussed in detail below. Once bleeding is definitively controlled by surgery, angiography, or the passage of time the goals for resuscitation become simpler. The goal of late resuscitation is to restore adequate cardiac output, while facilitating stabilization of vital signs, laboratory values, and blood composition. Further fluid therapy after the resolution of haemorrhage should be guided by monitors and measures, including invasive or non-invasive assessments of cardiac output and tissue perfusion, and serial assessment of arterial blood gases and serum lactate.[17] It is worth noting that many previously healthy trauma patients will achieve normal vital signs after haemorrhage while still being substantially under-perfused. This phenomenon, known as occult hypoperfusion, creates the potential for ongoing ischaemic injury if it is not recognized by more advanced laboratory or diagnostic monitoring.[18]

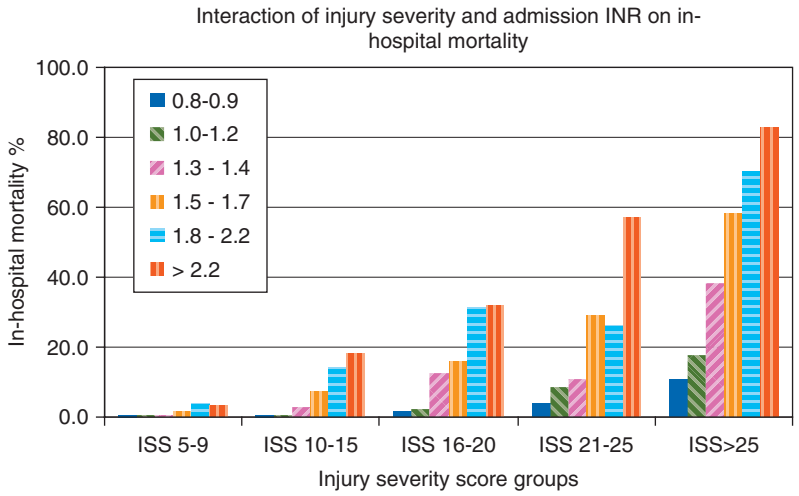

Fig 2 Hospital mortality as a function of injury severity and coagulation status at the time of trauma centre admission. INR, international normalized ratio; ISS, injury severity score. Reproduced with permission from Hess and colleagues.[7]

Table 1 Elements of haemostatic resuscitation, and level of evidence in support

Recommendation	Evidence
Expedited anatomic control	Strong; widely accepted
Deliberate hypotension	Several prospective trials; widely accepted
Early support of coagulation	
Antifibrinolytic therapy	One large prospective trial, several smaller studies; an emerging standard
Early use of plasma and platelets	Controversial; variable application in clinical practice
Vasodilation with anaesthetic agents	Theory only—minimal clinical data

Expedited 'damage control' surgery

The concept of damage control is adopted from the US Navy, which espoused the theory that response to catastrophe should be prioritized to keeping the ship afloat. In medical terms, this means a hierarchy of resuscitative efforts aimed at keeping the patient alive long enough to reach the next level of care. For pre-hospital care, especially in the military, there has been an increased focus on early control of exsanguinating haemorrhage and more widespread use of arterial tourniquets.[19] In the operating theatre, this theory dictates that initial surgery on a haemodynamically unstable, actively bleeding trauma patient should be focused on anatomic control of bleeding, with repair of less significant or time-critical procedures deferred until resuscitation is completed.[20] The patient undergoing exploratory laparotomy, for example, will have wide abdominal exposure, packing, ligation of bleeding vessels, and rapid excision of badly damaged solid organs. Bowel injuries will be managed by stapler control of contamination, without attempted reconstruction. Definitive closure will be deferred in favour of packing and temporary coverage with a sterile drape. Associated long-bone or pelvic fractures will be externally stabilized.[21] Once haemostasis is achieved, the patient is transferred to the intensive care unit for completion of resuscitation. Damage control is intended to minimize operating theatre time, minimize ongoing fluid administration, and preserve normothermia, thus reducing the secondary surgical and inflammatory insult that would arise from extensive bowel or soft-tissue reconstruction, orthopaedic manipulation, or other less essential procedures.

The value of rapid control of ongoing haemorrhage has substantial face validity, and is not controversial. The damage control approach has been studied a number of times and found to be beneficial.[22] While details vary from patient to patient and institution to institution, the overall philosophy is widely accepted and applied in both military and civilian care. For the anaesthesiologist, the value of expediting surgery is likely to outweigh normal considerations for elective surgery. Fasting time is not relevant because the risk of exsanguination or ischaemic organ failure is far greater than that of aspiration. Delaying surgery to obtain laboratory or radiological studies, await crossmatched blood products, or place invasive monitors is contraindicated. Instead, these activities should occur in parallel with the central activity of getting the patient to theatre and getting the surgery started.

Deliberate hypotension

During active haemorrhage, any fluid administration which increases arterial pressure will also increase blood loss. This

was observed during the first widespread use of i.v. fluid therapy for resuscitation, in World War I. Dr Walter Cannon, a US Army surgeon, noted 'Injection of a fluid that will increase blood pressure has dangers in itself. . . . If the pressure is raised before the surgeon is ready to check any bleeding that might take place, blood that is sorely needed may be lost'.[11] There is more at work in this phenomenon than passive physics. Fluid administration leads to increased venous return to the heart, which increases myocardial wall tension and acts through the Frank–Starling law to increase cardiac output. Increased cardiac output reduces the reflex vasoconstriction of haemorrhagic shock, allowing increased blood flow into injured vascular beds.[23] Increased pressure will also disrupt and wash away the extraluminal clots which initially limit haemorrhage.[12] Any asanguineous fluid used for resuscitation will decrease blood viscosity and will dilute the concentration of clotting factors, red blood cells (RBCs), and platelets at the site of haemorrhage.

The distinction between controlled haemorrhage, as in the classic Wiggers model, and uncontrolled haemorrhage was first explored in animal models in the 1990s. Results from multiple resuscitation trials in pigs,[24 23] rats,[25] dogs,[26] and sheep[27] demonstrated that blood loss was reduced during hypotension. Survival was improved with resuscitation strategies that limited the amount of fluid administered or titrated it to a lower than normal mean arterial pressure. Attempting to achieve normotension during active haemorrhage consistently increased mortality.[28]

Two prospective randomized human trials of deliberate hypotensive resuscitation were conducted in the 1990s, and a third is underway now. The first trial, a landmark in the history of resuscitation research, was published in 1994.[29] Five hundred and ninety-eight hypotensive victims of penetrating thoracoabdominal trauma were randomized at the scene of injury to conventional fluid therapy or minimal fluid therapy during the pre-hospital and emergency department (ED) phases of care. The cohort given minimal fluid had a significant survival advantage (70% *vs* 62%, $P=0.04$). A second trial randomized 110 hypotensive trauma patients to ED and operating theatre management targeted to a mean pressure of 60 *vs* 80 mm Hg until the definitive control of haemorrhage.[30] There was no difference in survival between the groups. Preliminary results from the third trial, underway now, show a beneficial effect of limiting administered fluid.[31]

The majority of experimental evidence and clinical experience over the past two decades suggest that a lower than normal arterial pressure should be targeted during early resuscitation. Advantages include reduced bleeding, more rapid haemostasis, and better preservation of native coagulation. Disadvantages are a delay in reperfusion of ischaemic tissue and a prolonged state of shock. Questions remain about the safe duration of deliberate hypotension (e.g. during prolonged transport from a rural area)[32] and about the risk:benefit relationship in high-risk patients (e.g. those with underlying cardiovascular disease, older age, or fresh traumatic brain injury). These patients are likely more vulnerable to ischaemic injury with low arterial pressure,[33] but these patients are also at greater risk from longer and more massive haemorrhage. The heterogeneous nature of traumatic injury makes it unlikely that specific human trials will be easy to accomplish, but the growth of trauma registry reporting may make observational inference possible in the near future.

Support of coagulation

Profound and irreversible coagulopathy is a universal finding in trauma patients who die of exsanguination after reaching the trauma centre alive.[9] Better understanding of the mechanisms involved, as described above, has led to resuscitation strategies emphasizing early support of coagulation. In practice, this means earlier and more aggressive transfusion of plasma, platelets, and factor concentrates. Clinicians now recognize that to be successful, transfusion therapy must often begin before a clear picture of the patient's injuries and physiology is available. This philosophy is reflected most clearly in the battlefield resuscitation algorithms now followed by both British[34] and American[35] forces operating in Afghanistan, but elements of this approach have influenced civilian trauma practice as well.[36] Care begins with control of any significant external haemorrhage. Direct pressure to the wound is the first approach—potentially supplemented by a haemostatic bandage—followed by tourniquet application when necessary and feasible. Arterial pressure is allowed to remain low as long as there is evidence of critical organ perfusion (i.e. mentation). Crystalloid or colloid fluid administration is minimized in favour of RBC and plasma administered in approximately equal quantities. An antifibrinolytic agent, typically tranexamic acid, is given as soon as potentially lethal haemorrhage is suspected.[37]

Logistics are the key to early support of coagulation. The need to expedite delivery of RBC and plasma has led to development of massive transfusion protocols (MTPs) in most large trauma centres.[38] These deliver set quantities of RBC, plasma, platelets, and sometimes adjuvant agents to the bedside, often in response to a single phone call or computerized order. Uncrossmatched type-O RBCs have an excellent safety record and are the resuscitation product of choice in any trauma patient in severe haemorrhagic shock.[39] Universal donor plasma is more difficult to provide because of the relative scarcity of type AB blood and the time required to thaw fresh-frozen units; a number of high-volume trauma centres have overcome this barrier by stockpiling plasma in liquid form.[40] In military practice, it is possible to obtain fresh whole blood from available donors who have been pre-screened for viral disease,[41] but this approach has not been replicated in civilian hospitals in the USA or Great Britain. Studies on the effectiveness of MTPs are almost uniformly positive; however, the data supporting their value are observational, and usually based on before-and-after methodology in single centres. It makes good intuitive sense, however, that making blood products more readily available at the bedside will improve resuscitation.

The optimal ratio of plasma to RBC units is controversial. Fresh whole blood, the ideal resuscitative fluid, has a ratio of 1:1. Component therapy designed to replicate this can achieve only marginally acceptable levels of RBC, clotting factors, and platelets when the deleterious effects of dilution and storage loss are considered (Fig. 3),[42] suggesting that any imbalance of one component over another will lead to a critical deficiency. Examination of transfusion practice in large trauma populations demonstrates that overall annual use of plasma and RBC units will be about equal, while retrospectively examining use in patients who survive a massive transfusion (more than 10 units of RBC in 24 h) also demonstrates equal overall requirements for plasma and RBC.[43] It is worth noting that coagulation factor activity of plasma units can vary, and that some of this variation may be averaged out when a larger number of units are given. Other arguments in favour of earlier and more vigorous use of plasma include the observation of Chowdary and colleagues[44] that relatively large amounts are required for haemostasis, and the previously reported antifibrinolytic activity of plasma compared with normal saline fluid therapy.[45] All of these observations suggest that 1:1 might be a logical starting point for transfusion when the severity of haemorrhage is such that resuscitation must begin before laboratory values are available.

Clinical evidence to support this theory is mixed. Unadjusted retrospective studies of mortality demonstrate a strong association between survival and increased administration of plasma,[46] but these studies are flawed by the heterogeneous nature of the patients included and the real-world logistics of transfusion. More severely injured patients are bleeding faster, and are more likely to die after receiving RBC but before plasma can reach the bedside. When survival bias is accounted for, results are equivocal.[47] A recent review of more than 20 studies of plasma:RBC ratio in clinical practice made this phenomenon clear;[48] studies that attempt to control for survival bias show mixed results, with some demonstrating a mild benefit to increasing plasma ratio and others showing no effect. The most recent published work in this area used the concept of instantaneous plasma deficit (RBC units–plasma units) in surviving patients at each hour after trauma centre admission to show that a smaller deficit was associated with improved survival, but only in the first 2 h of care.[49] More than anything, this study demonstrated the time-dependent nature of acute haemorrhagic shock. To date, no prospective trials comparing different resuscitation ratios have been published, although several are now underway.

Critics of ratio-based resuscitation algorithms note that different patients, with different injuries, must logically require different treatments. Distrust of the empiric approach has lent increased urgency to improving the speed and specificity of early diagnostic technology. For actively bleeding patients, this means point-of-care coagulation testing. Several studies of the use of whole-blood viscoelastic testing to guide resuscitation are now underway, and preliminary results are encouraging. Unlike traditional prothrombin time and partial thromboplastin time testing, viscoelastic tests can also assess some aspects of platelet function, fibrinogen level, and fibrinolysis. Viscoelastic testing may also be used to guide factor-based resuscitation. Rather than 'shotgun therapy' with plasma, some centres are studying directed administration of prothrombin-complex concentrates, fibrinogen, other single-factor concentrates (e.g. factor VIIa), and platelets.[50 51] It remains to be seen if this approach will provide more rapid haemostasis or reduce the long-term morbidities associated with plasma transfusion.

Early support of coagulation includes administration of an antifibrinolytic compound, typically tranexamic acid, in an

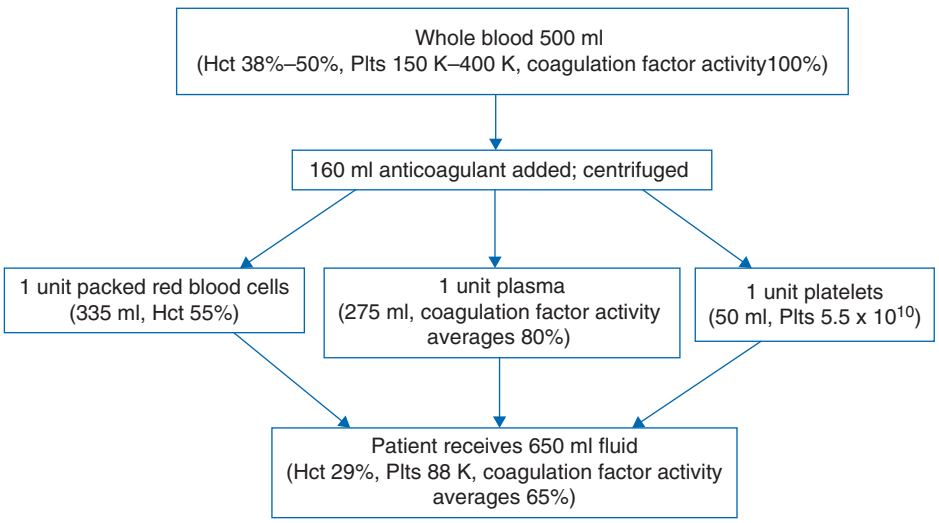

Fig 3 Dilution and storage loss reduce the effectiveness of component blood product therapy compared with fresh whole blood. Adopted from Armand and Hess with permission.[42]

effort to preserve clot stability during resuscitation. The very large CRASH-2 trial randomized 20 000 trauma patients worldwide to receive either placebo or tranexamic acid within hours of admission, and demonstrated a significant survival benefit with this therapy.[52] Curiously, there was no difference in transfusion requirements between the groups, suggesting that tranexamic acid may have effects in addition to antifibrinolysis. The earlier the drug was administered, the more positive the effect. An observational trial from the battlefield has corroborated the findings of CRASH-2,[37] and most trauma centres worldwide now include this step in their trauma resuscitation protocol.

Restoring tissue perfusion

One component of modern resuscitation practice has been postulated as beneficial, and included in military and civilian algorithms,[34 53] but never effectively studied. This is the early and aggressive administration of anaesthetic agents to reduce sympathetic outflow and dilate constricted vascular beds. In a perfect world, one in which anaesthetics did not have side-effects, every trauma patient would be deeply anaesthetized during ED assessment and damage control surgery. This approach has emotional and psychological benefits, and is what most prospective patients would strongly prefer. Unfortunately, any medication which reduces consciousness or pain will also reduce sympathetic outflow, and thus cardiac output.[54] Many common anaesthetics—propofol, midazolam, the volatile gases—are direct vasodilators and negative inotropes, but even those that are relatively 'safe' in euvolaemic patients (e.g. ketamine, opioids, etomidate) can cause precipitous hypotension and even pulseless cardiac arrest when administered to a patient in haemorrhagic shock. The hypotensive consequences of both direct vasodilation and indirect reduction in catecholamine release are further exacerbated by intubation and institution of positive pressure ventilation.

Concern with making a bad situation worse limits the depth of anaesthesia provided to unstable trauma patients in many centres. There have been no controlled studies assessing anaesthetic depth with brain-activity monitors during severe haemorrhage, but it is not unusual to observe haemorrhagic shock patients in the operating theatre who have received only small doses of an amnestic (e.g. scopolamine), a neuromuscular blocking agent, and no other analgesics or sedatives. While this does allow for preservation of native vasoconstrictive mechanisms, and thus more arterial pressure with less fluid administered, it is also sustaining the pathophysiology of shock: profound tissue and organ system ischaemia. It is possible that long-term outcomes will be improved by titrated administration of fluids and anaesthetics, targeting a high-flow, low-pressure vasodilated state that restores tissue perfusion without raising arterial pressure high enough to increase bleeding. With modern i.v. access, rapid infusion devices, and fast-onset medications, the anaesthesiologist has the capability to perform this titration in real time, for example, alternating small boluses of fluid (200 ml) with small doses of fentanyl (50–100 μg) until a deep level of anaesthesia is attained. This would allow for increased tissue perfusion, leading to less release of fibrinolytic and inflammatory compounds, without increasing the rate of haemorrhage.

This theory is rooted in the pathophysiology of shock. It explains the observed difference in perioperative survival for equivalent degrees of massive transfusion between trauma patients (11% in a recent study)[53] and elective surgery patients (2–5%).[55] It may also explain some of the improved survival seen in animal models of deliberate hypotension, relative to human studies, because experimental animals must be adequately anaesthetized (for both ethical and logistic reasons). To date, however, there are no clinical studies which have evaluated the early use of deep anaesthesia in trauma patients.

Current and future research directions

The following list summarizes controversial issues in resuscitation practice, and areas of ongoing research:

- Definition of the acceptable depth and duration of deliberate hypotension; development of 'shock monitors' that can help guide resuscitation.
- Comparison of plasma:platelet:RBC ratios for empiric resuscitation, and assessment of the risk:benefit ratio for transfusion therapy in general.
- The ideal role for isolated factor and platelet products.
- Development of point-of-care coagulation monitors; validation of their ability to improve outcomes.
- Further study of endothelial function during haemorrhagic shock and recovery.
- Study of the use of anaesthetic agents during resuscitation, and the impact of depth of anaesthesia on survival and morbidity.

Conclusion

Ideal resuscitation for the actively haemorrhaging trauma patient has evolved rapidly in the past decade, and will continue to change in the years to come. Volume replacement, transfusion of blood products, inflammatory mediation, and anaesthetic management are all important to outcome, and all deserving of further clinical study. Data from military and civilian trauma care suggest that outcomes are improving,[56 57 58] a trend that will continue with further research in this active area of clinical science.

Declaration of interest

R.P.D. has recently served on the Data Monitoring Committee for a clinical resuscitation trial using MPOX4, an oxygen therapeutic manufactured by Sangart, Inc.

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