Review

Resuscitation and coagulation in the severely injured trauma patient

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Developments in the resuscitation of the severely injured trauma patient in the last decade have been through the increased understanding of the early pathophysiological consequences of injury together with some observations and experiences of recent casualties of conflict. In particular, the recognition of early derangements of haemostasis with hypocoagulopathy being associated with increased mortality and morbidity and the prime importance of tissue hypoperfusion as a central driver to this process in this population of patients has led to new resuscitation strategies. These strategies have focused on haemostatic resuscitation and the development of the ideas of damage control resuscitation and damage control surgery continuum. This in turn has led to a requirement to be able to more closely monitor the physiological status, of major trauma patients, including their coagulation status, and react in an anticipatory fashion.

Keywords: damage control; massive transfusion; coagulopathy; viscoelastic; near-infrared spectroscopy; tissue oxygenation

1. INTRODUCTION

Every decade brings new understanding into aspects of the pathophysiology of shock, the underlying mechanisms and the consequences for optimizing management strategies. The last 10 years has been no exception, and in particular the recognition and understanding of the derangement in the coagulation status of shocked trauma patients have given new insights into how such patients should be assessed and managed. This article reviews some current thinking, dilemmas and experiences, and draws on some lessons and observations of managing the severely injured combat casualties.

2. VOLUME RESUSCITATION IN MAJOR TRAUMA

Haemorrhage is the leading cause of battlefield deaths [1] and the second leading cause after head injury of civilian trauma deaths [2]. Fluid resuscitation following trauma is frequently required to replace lost blood volume and optimize haemodynamics in order to maintain oxygen delivery to the tissues.

Over the last two decades, there has been a move towards hypotensive fluid-resuscitation strategies for trauma victims prior to surgical haemorrhage control. This has been based on laboratory findings in animal models and clinical data [3–5]. The rationale behind this approach to resuscitation is to avoid disrupting

the initial clot in the first hour after injury while it gains strength and before surgical control is achieved. This hypotensive approach has been adopted in civilian [6] and military [7] authority publications, advocating limited initial fluid resuscitation to resuscitate the trauma casualty in order to maintain a target systolic blood pressure of 80 mmHg (approximating to a palpable radial pulse). A systematic review of animal studies concluded that all the studies of hypotensive resuscitation strategies reduced the risk of death when compared with normotensive strategies [8]. However, the vascular injury used (e.g. a lesion in a major vessel such as the aorta or vascular transection) in these models maximized the risk of re-bleeding and therefore biased the findings in favour of hypotensive strategies. None of the studies continued the hypotensive resuscitation strategy beyond 120 min. A randomized controlled clinical trial of hypotensive versus normotensive resuscitation found no difference in survival between the groups [9]. The penalty for the hypotensive approach, especially if there is a prolonged time to surgical control and restoration of blood pressure, is a tissue hypoperfusion. A balance must be drawn between the effects of this and the risk of clot disruption. There is also a potential conflict in this approach with the multiple injured casualty, where the injury complex includes a head injury and hypotension needs to be avoided to prevent cerebral hypoperfusion and secondary brain injury.

Protracted hypotensive resuscitation has been shown to have adverse fatal consequences in a swine model of primary blast injury with haemorrhage [10]. In this study, animals were divided into four groups. All groups received a controlled haemorrhage and received

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Electronic supplementary material is available at <http://dx.doi.org/10.1098/rstb.2010.0220> or via <http://rstb.royalsocietypublishing.org>.

One contribution of 20 to a Theme Issue 'Military medicine in the 21st century: pushing the boundaries of combat casualty care'.

either normotensive or hypotensive resuscitation with or without a blast injury. Animals that received hypotensive resuscitation had a persistent acidosis compared with those animals that had normotensive resuscitation, regardless of the presence of blast in the normotensive group. This implies that prolonged hypotension will result in deleterious physiological consequences. These consequences were fatal in the blast-exposed animals. In this model, there was no possibility of re-bleeding; it was purely focused on the normotensive versus hypotensive strategies for resuscitation.

A further study using a blast injury and haemorrhage model in swine has examined the consequences of prolonged hypotensive resuscitation [11]. In this model, a controlled 30 per cent haemorrhage was followed by a liver injury to allow an injury at risk of re-bleeding. The initial hour of resuscitation was hypotensive in order to allow a good quality clot to form, and then the animals were divided into continued prolonged hypotensive resuscitation or a normotensive resuscitation. The resuscitation fluid was 0.9 per cent saline to maintain a blood pressure of either 80 mmHg (initial and prolonged hypotensive strategy) or 120 mmHg systolic (normotensive strategy after initial hour of hypotensive resuscitation, termed novel hybrid (NH) resuscitation). An increased survival to 8 h was observed, with no evidence of re-bleeding in the NH group. The worsening acidosis that was seen in the prolonged hypotensive resuscitation group was reversed in the NH group.

These experiments illustrate the need to consider the systemic, time-critical physiological consequences of using blood pressure-directed resuscitation strategies. There is a requirement to monitor these potential adverse physiological consequences in order to adjust the resuscitation strategy to ameliorate their effects on the outcome. The parameters used to monitor these physiological consequences may be used as endpoints or goals for the resuscitation strategy in themselves.

Endpoints for fluid resuscitation in haemorrhagic shock have been reviewed by Revell *et al.* [12], examining both blood pressure endpoints and fluid type (hypertonic versus isotonic) in human studies and animal models. They recognized that human data allowed only broad interpretations to be drawn and that the optimal fluid resuscitations have not been clearly established. They state that with the current evidence available, it is unclear if intravenous fluid replacement of lost circulating volume should be withheld completely until haemostasis is achieved or low volumes of fluid replacement should be given to a sub-normotensive blood pressure endpoint. The lower limits of permissive hypotension have not been established. It is also important to bear in mind that hypoperfusion can exist with normotensive blood pressure.

Much of the above work has focused on the pre-surgical control of haemorrhage and with blood pressure as an endpoint for resuscitation (hypo or normotensive). However, there are other important considerations in the resuscitation of major trauma patients. In haemorrhage resulting from, for example, a simple disruption to a readily accessible single vessel, it may be possible to arrest the bleeding with simple measures and without the casualty becoming

physiologically compromised. In severe polytrauma, however, there will be a complex of injuries that will not be amenable to simple measures and will result in significant physiological derangement. Some of these injuries may present competing resuscitation demands, for example, a patient with a head injury where one wishes to maintain the cerebral perfusion pressure and avoid hypotension combined with a major intracavity haemorrhage where a hypotensive strategy may be indicated initially. In such circumstances, in addition to volume replacement therapy, there are two other considerations: firstly the question of the innate haemostasis by the coagulation pathways and secondly, potentially linked with this, is tissue oxygen delivery (both globally and to vital organs such as the brain) as a resuscitation goal.

Initially, the fluid loss in major trauma is whole blood, with both the plasma and cellular fractions being lost. Replacement may be by blood, blood products or other fluids to restore volume. The type of fluid used in initial resuscitation is clearly an important consideration. While not the focus for this review, when blood derivatives are not used, the most commonly used classes of fluids are crystalloids or colloid solutions. Although artificial blood products have been developed to give an oxygen carrying capacity [13], these have not yet gained widespread clinical usage. Most non-blood-product fluid replacement is given to restore intravascular volume with an aim to achieve a given pressure goal, despite the inherent uncertainty about what this goal should be initially as discussed above. Crystalloids and colloids each have had their proponents and debate has been vigorous. A systematic review of randomized controlled trials, including many trauma trials [14] comparing resuscitation in critically ill patients with colloid versus crystalloid solutions, found that resuscitation with colloids was associated with an increased absolute risk of mortality and concluded that there was no evidence to support the continued use of colloid for volume replacement in resuscitation of the critically ill patient. The clinical effectiveness of pre-hospital intravenous fluid resuscitation in trauma patients has been examined in 2004 as part of The Health Technology Assessment Programme [15]. This concluded that there was no evidence that pre-hospital fluids were beneficial and indeed some evidence that they may be harmful. Blood and blood products were not examined in this assessment. Some resuscitation fluids are given for their other properties such as the anti-inflammatory properties of hypertonic saline dextran (HSD) [16,17]. This also has the effect of being able to restore blood pressure with smaller volumes of infused fluid than isotonic fluid replacement such as 0.9 per cent saline. Whether this is desirable is debatable given the potential risk of re-bleeding and the non-replacement of coagulation capability. The efficacy of HSD resuscitation for patients with hypotension following penetrating trauma was examined in a blinded study [18]. It was found that HSD resulted in an increase in blood pressure, reduction in haematocrit and with no differences in clotting indices. There was a significant improvement in survival in the HSD group. However, of particular significance in the military

Figure 1. The cell-based theory of coagulation. PLT, platelet; TF, tissue factor.

context, HSD was found to be an ineffective fluid for resuscitation after thoracic blast injury with haemorrhage in an animal model [19].

In addition to replacing the lost intravascular volume secondary to haemorrhage, it is necessary to ensure that haemostasis is maintained. It is recognized that major trauma can be associated with deranged coagulation. There is evidence from human volunteer studies that saline-induced haemodilution, as well as decreasing the concentration of plasma clotting factors, induces a pro-fibrinolytic state by decreasing anti-fibrinolytic proteins α_2 antiplasmin and thrombin activatable fibrinolysis inhibitor [20]. Fresh frozen plasma (FFP) was shown to ameliorate this pro-fibrinolytic state. Consideration of both volume replacement and maintenance of haemostasis is vital in resuscitating trauma patients.

3. TRAUMA-INDUCED COAGULOPATHY

Trauma coagulopathy has been described only relatively recently, but it has been shown that a trauma patient coagulopathic at admission to hospital is more likely to require massive blood transfusion, develop multi-organ failure (MOF) and have up to a fourfold chance of dying. In 2003, Brohi *et al.* [21] studied 1088 of 1867 trauma patients admitted to the Royal London Hospital between 1993 and 1998. This was a standard UK civilian major trauma population with 75 per cent blunt trauma with a median injury severity score (ISS) of 20. It was found that 24.4 per cent of patients had a coagulopathy on admission as defined by prothrombin time (PT) or activated partial thromboplastin time (aPTT) of 1.5 times normal. Median pre-hospital times were 73 min and median pre-hospital fluid administration was 800 ml. Patients with a coagulopathy had a median volume of 700 ml and those without coagulopathy a median

value of 1000 ml. The presence of coagulopathy was not found to be related to fluid administration.

As ISS increased, so did the number of patients with coagulopathy. Age and mechanism of injury had no effect on presence of coagulopathy. The overall mortality rate was 19.5 per cent. However, mortality was associated with the presence of coagulopathy (mortality in coagulopathic patients 46% versus 10.9% in non-coagulopathic patients) but statistically independent of ISS.

This important study demonstrated that there is an acute coagulopathy early in trauma, which is not related to dilution but is related to ISS and confers an increased mortality that is independent of ISS.

These findings are confirmed by studies from the USA [22] and Germany [23].

In the US study, Macleod *et al.* [22] reviewed prospectively collected data from 20 103 trauma patients admitted to the University of Miami/Jackson Memorial hospital, FL, USA between 1995 and 2000, of whom 7638 had complete datasets for final analysis. The population was similar to that of the Royal London study, although the median ISS and mortality rate were lower, with median ISS of 9 and overall mortality of 8.9 per cent. Coagulopathy was defined as those with an abnormal PT or abnormal aPTT. Patients with a normal PT had a mortality of 6.3 per cent, and those with an abnormal PT 19.3 per cent. This study showed that 28 per cent of trauma patients are coagulopathic on admission to hospital and they have an increased risk of early death.

Maegle *et al.* [23] retrospectively examined 17 200 trauma cases from the German trauma registry of which 8724 entries had complete data on coagulopathy. The population was very similar to the London and US populations, although 96 per cent had blunt trauma. He found that 34.2 per cent of patients were coagulopathic. The definition of coagulopathy differed from the previous studies, however, and was defined as

Figure 2. Acute traumatic coagulopathy: activated protein C-mediated coagulopathy.

a PT $<70\%$ and/or platelet count $<100\,000\,\mu\text{l}^{-1}$. Using this definition, coagulopathy also increased with ISS and mortality was increased in the coagulopathic group. It was shown that the coagulopathic patient group had a statistically significant increase in MOF, ventilator-dependent days, and ICU length of stay and hospital length of stay. The pre-hospital fluid administration volume findings were different from those of the two previous studies. The coagulopathic group received a mean of 2198 ml, and the non-coagulopathic group 1372 ml. Also, as the volume of pre-hospital fluid increased, so did the numbers with coagulopathy, although 10 per cent of coagulopathic patients received less than 500 ml. The conclusions from this study were much the same as Brohi's and MacLeod's, namely that coagulopathy on admission increased mortality independent of ISS, and as ISS increased so did the presence of coagulopathy and mortality. However, unlike Brohi's findings, the amount of pre-hospital fluid administration had an effect on the presence of coagulopathy. Despite the three studies having differing definitions of coagulopathy, they all find that approximately one-third of major trauma patients arriving at the emergency department are coagulopathic on admission to hospital, and that the presence of coagulopathy is associated with increased mortality. Variation in the definition of coagulopathy presents a problem in not only comparing studies but identifying patients and monitoring therapy. The common definitions quoted in the literature, such as PT greater than 18 s or aPTT greater than 60 s [24,25], or international normalized ratio (INR) greater than 1.5 [2] and PT/aPTT greater than 1.5 control values [26] depend on laboratory values that were designed to measure only the fluid phase of coagulation and not the factor and cellular components together and their interaction. It is timely, therefore to consider redefining what constitutes a coagulopathy in the trauma patient population using a more appropriate assessment of the coagulation pathway.

Central to the current coagulation theory is the cellular component of blood rather than just the more classical view of a plasma-borne factor cascade to produce fibrin [27]. The goal of haemostasis is to produce a stable clot formed of fibrin and platelets. The

Figure 3. (a) Classical damage control resuscitation–damage control surgery sequence. (b) Integrated damage control resuscitation–damage control surgery sequencing.

haemostatic process is divided into three phases—initiation, amplification and propagation (figure 1). Clot initiation occurs when extravascular tissue factor, present after injury, combines with factor VIIa. Factor VIIa is the only coagulation factor present in its active form in the blood. This activates factors V, IX and X and produces a small amount of thrombin. In the presence of platelets, this thrombin will cleave von Willebrand's factor (vWF) and factor VIII, activates factors V and XI and cause platelet activation. This is the amplification phase. Only once platelet activation occurs can a thrombin burst be generated causing insoluble fibrin to be produced in the propagation phase. Platelets have the central role in this cell-based clotting theory. This requires metabolically active platelets for activation and aggregation. Without the platelet surface being available at the site of injury, factor Xa and thrombin diffuse away from the site and are rapidly inactivated. This factor inactivation, combined with fibrinolysis mediated by proteins C and S, localizes the clot to the site of injury rather than allowing uncontrolled coagulation throughout the whole vasculature. The central role of platelet function needs to be considered in the assessment of coagulation in trauma patients.

The cause or causes of trauma-induced coagulopathy (TIC) may be multi-factorial and still poorly understood. It is clear that shock can lead to acidosis, hypothermia and inflammation, all of which can effect coagulation [28,29]. None of this is new. However, recent work has postulated a theory of tissue hypoperfusion leading to a primary coagulopathy termed acute coagulopathy of trauma shock [28,30].

(a) Hypothermia

Hypothermia impairs the body's ability to clot. As the temperature falls, protease activity decreases [31]. Factor VII activity decreases linearly with temperature, retaining only 80 per cent of its activity at 33°C [32]. However, these effects are minor when compared with the effect of hypothermia on platelets. Platelet activation is decreased owing to a decrease in

interaction between vWF and collagen glycoproteins 1b and X (GPIIb/IIIa), which is absent below 30°C [33].

As core temperature drops, blood loss and mortality increases. A core temperature of 34°C is a critical point at which a significant alteration in platelet physiology occurs in trauma patients and at which enzyme activity decreases. Hypothermia is directly correlated to injury severity and an independent risk factor for mortality, reaching 100 per cent when core temperature is less than 32°C in patients undergoing a laparotomy [34,35]. Hypothermia leads to α -adrenergic stimulation with vasoconstriction, exacerbating any organ hypoperfusion which may be already present secondary to hypotension from the injury. This leads to worsening acidosis. Both hypothermia and acidosis may be further exacerbated by aggressive fluid resuscitation.

(b) *Acidosis*

Acidosis similarly significantly affects haemostasis. At a pH less than 7.4, a normal platelet will change internal structure and lose the ability to change shape [36]. Coagulation factors are all affected differently by acidosis and calcium binding site affinity is decreased. At pH 7.1, thrombin produced in clot propagation is decreased by 50 per cent, fibrinogen by 35 per cent and platelet count by 50 per cent [37].

(c) *Haemodilution*

Haemodilution can play a part in the development of coagulopathy. Resuscitation with crystalloid has been shown to dilute factors, and the use of colloids that expand plasma volume to a greater extent can dilute even further, as well as directly inhibiting coagulation pathways and inducing a profibrinolytic state [20]. Resuscitation with whole blood, devoid of clotting factors, will also have a dilution effect. On the other hand, it has been shown that infusion of 1 l of 0.9 per cent saline into healthy volunteers can enhance clotting [38].

(d) *Inflammation*

Trauma is a strong inducer of inflammation and the systemic inflammatory response syndrome (SIRS) is common after significant traumatic injury. SIRS secondary to trauma causes endothelial and complement activation [39,40]. One study has suggested that this leads to activation of the thrombomodulin–protein C pathway and thus to anticoagulation and fibrinolysis [41].

(e) *Acute trauma coagulopathy*

The various factors contributing to trauma coagulopathy may act at different time points. The early coagulopathy present at the time the patient is admitted to hospital occurs in approximately one-third of patients and appears to be related to shock [41] and tissue hypoperfusion. It occurs before the effects of acidosis, hypothermia and haemodilution. The terminology has been in evolution and the early coagulopathy has now been termed acute trauma coagulopathy (ATC) and the coagulopathy associated with this and subsequent acidosis, hypothermia and haemodilution as TIC [42], although there is currently no accepted consensus on these terms.

The proposed underlying driving mechanism for ATC is tissue hypoperfusion. In normal coagulation, thrombin formation leads to fibrinogen being converted to insoluble fibrin. Fibrin will in turn be broken down to its degradation products by the action of plasmin. Normal localization pathways include mopping up of thrombin by thrombomodulin to produce a thrombin–thrombomodulin complex (T–TM), thus stopping the activity of thrombin on fibrinogen. The T–TM complex activates protein C, which directly inhibits factors V and VIII on the platelet leading to less thrombin production. T–TM will also increase the effect of plasmin by removing inhibition of tissue plasminogen activator (tPA) on plasminogen. The overall effect is to produce anticoagulation and increased fibrinolysis (figure 2). It is postulated that ATC is a primary coagulopathy owing to pathologically enhanced activation of protein C (PC) as a consequence of tissue hypoperfusion, rather than a factor consumption effect.

To investigate this, a blinded study [41] of 208 major trauma patients, arriving at a single level 1 trauma centre, was conducted. The patients had a mean ISS of 17 and a median time from injury to blood sampling of 32 min. There was no vasopressor or colloid use and mean crystalloid administration was 150 ml. Platelet counts were normal in all patients. Hypoperfusion was judged to be present if there was a base deficit (BD) of 6 or less, and coagulopathy to be present if aPTT or PT were 1.5 times normal. As injury severity increased, so did the amount of thrombin generation, but the amount was unchanged as hypoperfusion increased. Coagulopathy occurred only if there was a BD < 6. It was found that a BD < 6 was associated with a rise in thrombomodulin levels and a fall in PC levels. Activated protein C (aPC) levels could not be measured and the assumption was that a drop in PC levels was because of a rise in conversion of PC to aPC. Thus, the hypothesis is that a greater BD reflects the tissue hypoperfusion leading to a rise in T–TM complexes, conversion of PC to aPC and therefore anticoagulation via inhibition of factors V and VIII. The fall in PC levels was also associated with a fall in plasminogen activator inhibitor 1 (PAI-1). PAI-1 inhibits tPA, so as PAI-1 levels fall, tPA activity increases and hyperfibrinolysis occurs. Hyperfibrinolysis in major trauma, as identified by thromboelastometry (TEM) in the emergency department, has been shown in a separate study to be an independent predictor of mortality itself [43].

The important implication from the Brohi study is that if ATC exists as a result of activation of the thrombomodulin–protein C pathway secondary to tissue hypoperfusion, then there is no failure of thrombin generation. Treatment of ATC would require reversing tissue hypoperfusion rather than simply treatment with blood component therapy. However, as discussed above, the permissive hypotensive resuscitation protocols will lead to relative tissue hypoperfusion and hence could potentially exacerbate the TIC and ATC.

The different mechanisms causing TIC have different implications for potential management strategies at different time points during the resuscitation of the trauma patient. Initially, it may be that ATC is related

to hypoperfusion and not abnormal clotting pathways or deficiencies in normal coagulation. Later on, the process may be driven by consumption or dilution. This may mean that the treatment goals are different depending on the underlying mechanism involved at that particular time point. Initial resuscitation may need to emphasize tissue oxygenation. It has been shown that early supplementary oxygen after blast injury and haemorrhage improved survival when a hypotensive resuscitation strategy was employed in an animal model [44]. Component therapy in the presence of tissue hypoxia might potentially worsen hyperfibrinolysis by increasing the available thrombin to conjugate with thrombomodulin, driving aPC production. Therefore, if initial hypotensive resuscitation leads to significant critical tissue hypoperfusion and hypoxia, it could exacerbate ATC.

Once a major trauma casualty arrives in hospital, the requirement for hypotensive resuscitation may no longer be pertinent if systems allow access to the rapid control of major surgical haemorrhage, as the concern over disruption of native clot will no longer pertain. Fluid and targeted therapy should be used in order to reverse tissue hypoxia and restore haemostasis. This is not always a trivial objective and requires the ability to closely monitor the patient's tissue oxygenation and coagulation status and changes that occur in these parameters as resuscitation, including surgical manoeuvres, proceeds. This requires clinically informed, real-time patient monitoring and evaluation in order to manage the transition through the resuscitation process including surgical haemorrhage control.

4. DAMAGE CONTROL RESUSCITATION– DAMAGE CONTROL SURGERY SEQUENCING

From the considerations of volume replacement and managing the ATC and TIC discussed above, the idea of damage control resuscitation (DCR) has been described. DCR is a concept developed from the philosophy of damage control surgery (DCS). DCS is an operative strategy that sacrifices the completeness of the immediate surgical repair in order to address the physiological consequences of the combined trauma of injury and surgery. In the past, this has been very much focused on abdominal trauma and the idea of performing an 'abbreviated laparotomy'. However, the concepts are applicable to injuries beyond the abdomen [45–47].

DCR has been developed in military trauma systems and has been defined as:

- proactive early treatment to address the lethal triad (by rapid reversal of acidosis, prevention of hypothermia and coagulopathy) on admission to combat hospital (by a US military group [48]); and
- as a systematic approach to major trauma combining the catastrophic bleeding, airway, breathing and circulation (<C>ABC) paradigm with a series of clinical techniques from point of wounding to definitive treatment in order to minimize blood loss, maximize tissue oxygenation and optimize outcome (by a UK military group [49]).

These two definitions, while expressing the DCR concept differently, require the same practical measures to achieve the aim of DCR, namely proactive management of the physiological consequences of the injury. The UK definition extends the DCR principle forward to the point of wounding and more explicitly recognizes the importance of tissue oxygenation. However, central to both is early recognition and management of the physiological consequences of the injury, including the acidosis associated with tissue hypoperfusion and the trauma-associated coagulopathy.

The principles of DCS have been well described for over 20 years but have been slow to gain universal acceptance. However, it is now recognized that severely injured trauma patients are more likely to die from the metabolic consequences of the injury rather than the completeness of the immediate surgical repair to damaged organs. While there has been academic recognition of the importance of addressing resuscitation and surgical issues concurrently, it is only with the development of the concept of DCR and the emergence of clinically useful technological tools that this integration has been consolidated into practice ([50]; figure 3a,b).

The most severely injured trauma patients represent only approximately 10 per cent of trauma cases but the majority of in-hospital trauma deaths. Damage control approaches are only relevant to this sub-population of trauma patients. Therefore, while 90 per cent of trauma patients are not in shock and are hypercoagulable rather than hypocoagulable following injury, the 10 per cent of patients most severely injured are in shock, and at risk of ATC and TIC [48]. It is in this group that DCR is required and massive transfusion anticipated.

5. MASSIVE HAEMORRHAGE PROTOCOLS

These new insights into the pathophysiological changes have influenced the approach to resuscitation. Massive haemorrhage protocols have developed to counter the dilution and consumption of clotting factors and addressing hypothermia and acidosis in patients with severe injury and massive haemorrhage. Historically, in the era when blood component therapy replaced whole blood transfusion, this was achieved primarily by transfusing plasma only after certain numbers of units of packed red blood cells (PRBC) had been given or when abnormal laboratory tests indicated a coagulopathy. Fibrinogen and platelets were given to correct abnormal plasma values or platelet counts from laboratory tests and normally after multiple units of PRBC and plasma. More recently, the recognition of the early presence of ATC before significant dilution or consumption of clotting factors has occurred mandates early recognition and prompt treatment in order to try and reduce the associated increased mortality in this group of patients. Recognition to date has been largely based on clinical indicators of injury severity and blood loss. These clinically based predictions perform with only about 80 per cent sensitivity and specificity [51]. Massive haemorrhage protocols to prevent the development of TIC have underpinned the delivery of DCR in

conjunction with improving tissue oxygenation and preventing hypothermia and ameliorating acidosis. Definitions of what constitutes a massive transfusion in the literature have varied. The transfusion of more than the patient's circulating volume in 24 h or more than 10 units PRBC in 24 h are most regularly cited [52]. The difficulty with these types of definition is that they are not anticipatory but reactive and that they summate the requirement over a 24 h period. An acutely haemorrhaging patient may require a relatively large transfusion initially within the first few hours, whereas others may accumulate the requisite number over the whole 24 h period. Are these two patient groups the same? In a study from the US [53], it was noted that the patients with severe injuries and at risk of life-threatening coagulopathy, 85 per cent of the transfusions were given in the first 6 h post-injury. It may be more sensible to adopt definitions with a shorter time interval for the transfusion requirement as the group truly having massive transfusion after trauma to allow appropriate comparisons of studies to be made.

A global review of centres receiving trauma patients found many without clear massive transfusion protocols [52]. Those with transfusion protocols have moved to adoption of high ratios of FFP to red blood cell (RBC) transfusion. The responsibility and mechanisms for declaring implementation of a massive transfusion protocol varied from centre to centre. UK Defence Medical Services (DMS) have adopted a pragmatic and responsive approach to declaring massive transfusion by adopting definitions that reflect haemorrhage at earlier time points than the blood given over a 24 h time period [54]. These are:

- blood loss of more than 150 ml min^{-1} ;
- transfusion of four units of red cells in 1 h; and
- replacement of 50 per cent of blood volume in 3 h.

The DMS massive haemorrhage policy may be implemented on clinical assessment of injury severity as follows:

- clinically obvious massive haemorrhage;
- bilateral proximal traumatic amputation;
- truncal bleeding and one proximal traumatic amputation;
- *plus* a temperature less than 35°C , systolic blood pressure less than 90 mmHg or abnormal mental state (and secondary supportive evidence from laboratory findings of INR greater than 1.5, BD greater than 6 and haemoglobin concentration of less than 11 g dl^{-1} , although these laboratory measures are not a requirement for activation of the protocol).

Eight recently published series, all retrospective studies, have suggested advantages with ratios of FFP:PRBC of 1:2 or greater [53,55–61]. One small prospective study failed to show improved outcome with a 1:1 ratio of FFP:PRBC [62]. It is noteworthy that in the German Registry study [56], the number of septic complications and incidence of MOF was higher in the group receiving 1:1 FFP:

PRBC transfusions, although this may be owing to confounding group differences. There has been a single systematic review of the literature [63], with an update in 2010 [64], which recognized the limited science on which to base recommendations but suggested a dose of $10\text{--}15 \text{ ml kg}^{-1}$ FFP transfusion for control of PT or aPTT of greater than 1.5 normal. In the updated review there is recognition that viscoelastic methods to assess coagulation may better guide therapy. With current concepts of coagulation theory, where platelets are the central driving force behind production of stable clot, plasma tests of specific factors (PT/aPTT) will not be accurate reflections of whole blood coagulation in rapidly changing situations.

In a retrospective analysis of data from a US Army Combat Support Hospital, it was found that in patients requiring massive transfusion (defined as 10 or more units RBC in 24 h), the ratio of plasma to RBC transfused was independently associated with survival to hospital discharge, primarily by decreased death from haemorrhage. Those receiving a high plasma to RBC ratio of 1:1.4 had improved survival compared with those receiving lower ratio transfusion [60]. This effect was independent of thoracic abbreviated injury score (AIS), admission haemoglobin concentration or use of recombinant factor VIIa (rFVIIa). Interestingly, this study also found that BD as a measure of acidosis secondary to tissue hypoperfusion, and AIS for head and neck injury were also independently associated with mortality. In addition, they observed that the hourly rate of administration of crystalloid and blood products was decreased in the patients receiving higher transfusion ratios.

A difficulty of all the retrospective studies is survival bias. Patients who receive high ratio of FFP:PRBC may be those that survive long enough to get the FFP. This confounding factor is recognized in some studies [60] but considered an unlikely explanation of the observation of the improved mortality by the authors, as the severity of injury between groups receiving different FFP:PRBC ratios were similar, as assessed by ISS, systolic blood pressure, BD and INR. However, others remain of the opinion that the benefits of high FFP:PRBC ratio and in particular 1:1 transfusion is acting as a surrogate marker of survival [65,66]. Other studies have suggested that blood transfusion is an independent prognostic factor associated with mortality even when adjusted for the severity of shock [67]. There are complex confounding factors including the age of the transfused blood. It has been shown that blood more than 14 days old, even when leucoreduced, is an independent predictor of mortality [68]. This makes it imperative that careful assessment of patients is performed rapidly to identify those who will benefit and not expose those who do not require transfusion, and to use PRBC less than 14 days old.

There are other therapies to be considered in correcting TIC. The central role of platelets in the cell-based theory of coagulation makes it imperative that their function is considered when resuscitating trauma patients. The contribution of platelet count and function in the formation of stable firm clot in the injured patient is not fully known. It is appreciated

that the function of the activated platelet in thrombin generation is both crucial and complex and that static absolute platelet counts are of little value in themselves [69,70]. Early use of platelets in massive haemorrhage protocols has been advocated [57,71] to the extent of transfusion goals of FFP:PRBC:platelet ratio of 1:1:1 being advocated. This is not universally supported, and others have considered platelet counts alone of greater than $100 \times 10^9 \text{ l}^{-1}$ are unlikely to be associated with coagulopathy and routine administration cannot be justified [65]. The most recent European guidelines for the management of bleeding following trauma base the platelet transfusion threshold on absolute platelet count [64].

Cryoprecipitate is the cold insoluble fraction formed when FFP is thawed. It is rich in factors VIII, XIII, vWF and fibrinogen and is given to replenish these, which are under-represented in thawed FFP. Being a pooled product, it does increase recipient donor exposure. It is commonly given when there is evidence of hypofibrinogenaemia, when plasma fibrinogen levels are less than $1.5\text{--}2.0 \text{ g l}^{-1}$ [64]. Similarly, fibrinogen concentrate may be given on the same basis. Interestingly, in a prospective study of 208 major trauma patients (median ISS of 17) [41], no patient had abnormal platelet or fibrinogen levels at presentation to the level 1 trauma centre despite a significant proportion exhibiting TIC. In a pig animal model, it has been shown that when clotting is assessed by rotational TEM, impaired clot formation in thrombocytopenia is improved with the administration of fibrinogen concentrate [72]. Recent guidelines advocate the use of TEM to assess the functional fibrinogen deficit and requirement for cryoprecipitate or fibrinogen concentrate [64].

The use of rFVIIa in trauma is still contentious and is off licence. The same literature review and guidelines as above recommend consideration in blunt trauma where haemorrhage persists despite standard attempts to control bleeding, and best practice transfusion of blood components.

Fibrinolysis can be a component of ATC. An international multi-centre randomized placebo-controlled trial of 20 000 patients evaluating the use of the anti-fibrinolytic tranexamic acid in major trauma within 8 h of injury safely reduced the risk of bleeding in trauma patients [73].

Treatment protocols have been based on a 'one size fits all' approach. Use of blood and plasma can be associated with adverse outcomes other than just those potential risks from exposure disease transmitted by blood products. There is evidence from a prospective multi-centre cohort study in trauma patients who survive their initial injury of FFP transfusion being independently associated with MOF and acute respiratory distress syndrome [74]. Also a pilot study in combat casualties has indicated that allogeneic blood transfusion was associated with increased peri-operative infection and impaired wound healing [75]. As discussed, the study from the German Trauma Registry [56] found increasing septic complications and MOF in patients receiving high FFP:PRBC ratios. Napolitano reviewed the cumulative risks of early RBC transfusion in trauma and considered the adverse

effects to be owing to increasing incidence of SIRS, immunomodulation and microcirculatory dysfunction [76]. However, haemostatic resuscitation during surgery with high ratios of FFP to PRBC in patients with TIC improves survival [77]. These studies emphasize the requirement to make a rapid diagnosis, hence appropriate treatment can be given and tailored to patients requiring haemostatic resuscitation and those patients not requiring such intervention are not exposed to the unnecessary risks.

6. POINT OF CARE TESTING AND MONITORING IN TRAUMA RESUSCITATION

Resuscitation of the severely injured trauma patient is a dynamic process with a potentially rapidly changing physiological condition of the patient. Therefore, the physiological data that is required to assess and monitor the patient's condition must also be rapidly responsive and rapidly accessible to the managing clinical team. Many laboratory measured parameters require time to send, analyse and return data to the clinical area, by which time the results are of historic interest as the patients' condition would have changed in the intervening interval. Point of care tests at or close to the patient in the treatment areas (emergency room, operating theatre or intensive care unit) minimize the time to test-result availability to the clinicians.

It is important to consider which physiological parameters are most relevant to assess and monitor the clinical status of the patient and effective resuscitation. A tenet of resuscitation of the severely injured trauma patient is restoration of adequate tissue perfusion and oxygenation in order to maintain cellular homeostasis. Tissue hypoperfusion may also drive the ATC through the aPC pathway. Restoration of adequate tissue perfusion must be achieved while addressing the drivers of TIC, namely hypothermia and haemodilution. The classical parameters of vital signs of blood pressure, heart rate, respiratory rate, capillary refill time, shock index (heart rate divided by systolic blood pressure) and urine output are low technology and minimally invasive assessment tools but are also poorly responsive to the degree and rate of haemorrhage, especially in the fit young population that characterizes the trauma patients, who have a physiological reserve that maintains these parameters until significant intravascular blood volume loss [78,79]. Neither do they directly relate to tissue oxygenation. Other endpoints such as mixed central venous oxygen ($S_{cv}O_2$), arterial lactate or lactate clearance, and arterial BD are intermittent and invasive [80]. Assessments of cardiac filling and stroke volume with techniques such as suprasternal notch Doppler ultrasound require technical expertise, which is then unavailable for other tasks, and have potential intra-observer variability. All of these parameters are surrogates for tissue perfusion and oxygenation. Pulse oximetry provides no information on peripheral tissue perfusion.

An ideal test would be a minimally invasive method of giving real time continuous direct measurement of tissue perfusion and oxygenation.

Near-infrared spectroscopy (NIRS) uses the transmission of light wavelengths of 700–1000 nm through skin, bone and muscle, and the different absorption spectra of oxyhaemoglobin and deoxyhaemoglobin to directly assess the degree of tissue oxygenation (StO₂). NIRS provides a potential non-invasive, continuous, reproducible methodology to assess tissue perfusion. It requires little training to apply and no technical expertise to perform. It has been shown to be more reliable than BD and S_vO₂ in a porcine model of shock and a potential sole endpoint for resuscitation monitoring [81]. A prospective non-randomized observational human study of volunteers and patients admitted to a level 1 trauma centre established a normal range for thenar eminence StO₂ and showed it could be used to identify the patients in severe shock. However, this study did not attempt to examine the effect of resuscitation on StO₂ [82]. A prospective, blinded cohort study of patients admitted to a level 1 trauma centre has demonstrated that initial StO₂ values correlated with shock index and was predictive of the development of subsequent multi-organ dysfunction syndrome [83]. This has been corroborated by other groups [84]. NIRS has also been shown to be able to assess blood loss intraoperatively and the effectiveness of resuscitation [85,86]. It has also been shown that StO₂ predicts the requirement for early blood transfusion in trauma patients [87]. NIRS has the added advantage in that it can measure cerebral StO₂; so in the case of concomitant head injury where cerebral hypoperfusion needs to be avoided (especially, where a permissive hypotensive resuscitation strategy is being adopted), this can be monitored during resuscitation. Thus, while there is no randomized-controlled trial showing that NIRS measurement of StO₂ can be used as an endpoint to assess resuscitation adequacy of a severely injured trauma patient leading to improved outcomes, it remains a candidate for a near patient test for this purpose and requires further evaluation.

The requirement for a rapid and reliable assessment of coagulation status of trauma patients has been made with the recognition of ATC occurring early after injury. This is necessary in order to identify the patients in whom ATC and TIC have developed and to avoid unnecessary exposure of patients to treatment who do not require it. There is also a requirement to be able to monitor the effect of treatment in a responsive and timely manner. Assessing coagulation status in trauma patients with standard laboratory tests such as PT and aPTT for TIC are insensitive for detecting ATC or monitoring the effects of therapy and have a significant lag behind the clinical picture owing to the time delay in their performance [37,88]. There are a number of global coagulation tests such as activated clotting time and bleeding time. Traditional clotting studies are not only an inaccurate reflection of what is the *in vivo* reality, but historical in terms of the patient's current coagulation status by the time the results are obtained.

Viscoelastic methodologies will provide a real-time dynamic interpretation of whole blood coagulation, with both cellular and factor components, and will provide a quicker result than sending a standard

clotting screen to the laboratory. The time taken for the result in a massive haemorrhage situation is crucial if there is an intention to intelligently manage an individual's coagulopathy. Two closely related viscoelastic methodologies are practically available for near-patient testing and monitoring. These are thromboelastography (TEG) and TEM. While they measure essentially the same parameters of clot initiation and dynamics of clot development, they do not produce absolutely equivalent results. A major advantage to this type of clinical coagulation assessment is that it allows the critical relative contribution of the functional platelets and factors to be analysed and can be used to guide specific replacement therapy. There is no standard accepted definition of clinical coagulopathy defined by TEM or TEG parameters. However, a strategy whereby the presence of two or more abnormal values from either clot initiation, clot dynamics or clot strength are regarded as hypocoagulable has been examined [89]. Using this, TEM has been shown to detect hypocoagulability within 10 min of clot initiation. The whole process of taking blood to having an indication of hypocoagulability will take 15 min and is available at the operating table or in the emergency department. Once treatment has started, TEM can be used to target therapy, minimizing the need for empirical products and maximizing the impact of administered platelets and fibrinogen. This ensures that the right patient has the right product at the right time. This, like NIRS, allows individual tailoring of the resuscitation strategy to the patient rather than adopting a completely protocolized management, which is an identical 'one size fits all' approach to patients. The exact positions of NIRS and TEG or TEM or other near-patient assessments of tissue perfusion and coagulation in resuscitation protocols have yet to be defined but the requirement is clear [13].

7. CONCLUDING REMARKS

The association between shock with tissue hypoperfusion and the development of ATC and the association of this with increased mortality and morbidity has led to a reassessment of the underlying principles involved in trauma resuscitation. While the importance of hypothermia, acidosis and haemodilution of clotting factors remains relevant in TIC, the recognition of the early development of ATC requires a fundamental reappraisal of the initial management of severely injured trauma patients. Many lessons can be drawn from observations and experiences from combat casualties in contemporary conflict zones. It is difficult to perform randomized-controlled trials in these environments but the study and observations from the management of these casualties have helped inform and develop ideas from civilian trauma studies [90]. The development of DCR and the sequencing with DCS have incorporated the principles of haemostatic resuscitation. The basis of this is the incorporation of mature massive haemorrhage protocols into resuscitation strategies. It has become clearer that tissue hypoperfusion remains a central driver to the pathophysiological consequences of shock

including ATC. This needs to be considered when adopting hypotensive resuscitation strategies. The development of new technologies has allowed the use of real-time, minimally invasive, near-patient assessments of both tissue oxygenation and whole blood coagulation. This opens up the prospect of evaluating some direct endpoints to guide management and individually tailoring early resuscitation therapies. The exact position of these measures within protocols has yet to be established.

With the understanding of the relative contribution of tissue hypoperfusion, ATC and TIC along the resuscitation pathway, a rational use of therapies and the monitoring of their effectiveness allow the clinical team to sequence the DCR–DCS process. This requires close integration of the team, with all members having an appreciation of the goals at any given time point. To successfully deliver effective DCR–DCS requires team understanding of the processes involved, training and a continuous dialogue between anaesthetic and surgical components of the surgical trauma team in order to react to the physiological response of the patient in the most appropriate and effective way.

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