Management of haemorrhage in major trauma

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Key points

Haemorrhagic shock is treated as a surgical emergency.

In-hospital treatment seamlessly integrates with pre-hospital treatment and multidisciplinary teams that should be well rehearsed.

The use of protocolized transfusion therapies should precede individualized treatment.

Restoration of normal physiology takes priority over the completeness of the surgical repair.

Prompt resuscitation may limit the overall inflammatory response including coagulopathy and improve outcomes.

Major trauma is a significant cause of death worldwide, leading to 5 million deaths annually. A large proportion of deaths are due to bleeding, with haemorrhage accounting for 80% of deaths in the operating theatre and 40% of all deaths from trauma within the UK.[1]

Treatment approaches to the management of major haemorrhage have transformed during recent decades, based mainly on retrospective evidence. Contemporary approaches emphasize rapid control of bleeding, early management of coagulopathy, maintenance of adequate perfusion, and minimizing the inflammatory response.[2] Developments in the early resuscitation phase and prevention or early management of coagulopathy combined with better understanding of point-of-care diagnostic tests are leading to more targeted interventions for haemorrhage control resulting in improved patient outcomes and less demand for blood products.[3]

Why does major haemorrhage cause problems?

Physiological response

Simple, uncontrolled haemorrhage leads to the development of hypovolaemia and shock. The physiological response is an initial tachycardia with increased systemic vascular resistance (SVR) to maintain arterial pressure (AP) despite a decreasing cardiac output. Once 20–30% blood volume is lost, bradycardia coupled with loss of SVR results in decreased AP. Continued blood loss exceeding 40% leads to a pre-terminal phase of increased sympathetic drive with tachycardia and hypotension. Superimposed trauma and pain will mask this reflex with less hypotension, thus there may be significant blood loss with a well-maintained AP.

Increased sympathetic tone diverts blood away from non-vital organs to maintain perfusion to vital organs, leading to hypoperfusion and inadequate oxygen delivery to the non-vital vascular beds and the microcirculation. Persistent, untreated hypoperfusion to the microcirculation will result in increased activation of the vascular endothelium, resulting in an exaggerated inflammatory response.[2] The microcirculation 'unit' consists of an arteriole, a capillary bed, and a venule and is particularly susceptible to hypoxic insults. The delivery of oxygen is dependent on blood flow, and increases in pre-capillary vasomotor tone either by endogenous catecholamines or by prescribed vasopressors will potentiate any hypoperfusion to the microcirculation and potentially worsen the inflammatory response.

Trauma-induced coagulopathy

Traditional resuscitation concentrated on the restoration of blood volume with crystalloid solutions in order to increase cardiac output. However, this often led to a lethal triad of acidosis, hypothermia, and coagulopathy. Indeed, it was noted in one series that up to 95% of trauma patients who died were coagulopathic. Resuscitation exclusively with crystalloids or synthetic colloids will inevitably lead to dilution of the patient's own clotting factors and haemoglobin resulting in a dilutional coagulopathy.[1] Activation of coagulation will lead to consumption of clotting factors, particularly factor V and fibrinogen, leading to a consumptive coagulopathy. Hypothermia and acidosis impair the functional ability of platelets and clotting factors, particularly below a pH of 7.1 and a temperature $<33^{\circ}$C. These effects are collectively called trauma-induced coagulopathy (TIC) and will occur during resuscitation if not mitigated for.[4]

In 2003, Brohi and colleagues[5] found that 24% of UK trauma patients were coagulopathic on arrival at the emergency department (ED) and the incidence of coagulopathy increased with severity of injury independent of the volume of pre-hospital resuscitation fluid. Those who arrived coagulopathic had an increased mortality compared with non-coagulopathic patients. This coagulopathy is termed acute trauma coagulopathy (ATC) and is another mechanism of coagulopathy under the umbrella term of TIC.

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The mechanisms of ATC are yet unproven but appear to be related to tissue hypoperfusion, leading to up-regulation of the vascular endothelium and subsequent alterations in coagulation pathways. This coincides with massive activation of coagulation with consumption of clotting factors, noticeably factor V and fibrinogen, activation of the Protein C pathway, and increased fibrinolysis.[4]

Inflammatory response to haemorrhage

Tissue hypoperfusion induces an inflammatory response characteristic of ischaemia–reperfusion injury. A range of inflammatory mediators, cytokines, and oxidants are released, which may lead to secondary organ damage associated with multiple-organ failure (MOF) and death. The systemic inflammatory response syndrome (SIRS) invokes a simultaneous compensatory anti-inflammatory response (CARS), leading to a reprioritization of cellular functions and suppression of adaptive immunity, the so-called 'genomic storm'. The extent and duration of the CARS and SIRS is related to the extent and duration of the initial inflammatory insult. Patients who recover their genomic expression in 2–3 days have uncomplicated recoveries, whereas those who do not have complicated recoveries.[2]

Some experimental models have looked at the generation and response of inflammatory mediators after resuscitation and have suggested that improving tissue oxygen delivery may have a beneficial effect on the inflammatory response and coagulation pathways.[6] This is backed up by some clinical evidence that resuscitation with blood products rather than a crystalloid-based resuscitation will dampen down the SIRS response after trauma and maintain endothelial integrity.

Thus, the current thinking of ATC implicates the inflammatory response driven by the hypoxic endothelium as the main driver of coagulopathy and the SIRS after trauma. It is reasonable to assume, therefore, that rapid reversal of tissue hypoxia and restoration of blood flow to the microcirculation will lead to a reduction in SIRS, the associated CARS, and potentially improved survival.

How should we resuscitate after haemorrhagic shock?

Damage control resuscitation

Damage control resuscitation (DCR) is a philosophy of surgical teams, concentrating on restoring a patients' physiology rather than completing surgical repair. This can only be achieved by well-rehearsed pre-hospital and surgical teams seamlessly interacting to stop bleeding, resuscitating the microcirculation, and mitigating against TIC.[7]

DCR incorporates the concept of haemostatic resuscitation (HR) where effective whole blood is transfused into the patient in its component parts. This effectively leads to a ratio of 1 fresh-frozen plasma (FFP):1 packed red blood cells (PRBC) with protocolized or targeted use of platelets and cryoprecipitate. Evidence for this is limited to retrospective military and civilian studies. The United Kingdom Defence Medical Services (UK DMS) massive haemorrhage policy supports the use of FFP and PRBC in a 1:1 ratio, together with administration of other blood components and tranexamic acid (TXA). Current practice is shown in Figure 1.

The appropriate ratio of FFP:PRBC and the amount and timing of platelet and cryoprecipitate administration has become increasingly less clear and the direct translation of military practice into civilian trauma is being challenged. Civilian data suggest that coagulation therapy, survival, and complication rates may be better at ratios nearer 1:2 (FFP:PRBC).[4] This uncertainty is reflected in the differing massive haemorrhage protocols (MHP) that exist throughout the country. What is well accepted, however, is that the 'new way' (high-ratio FFP:PRBC with earlier platelets and cryoprecipitate) is better than the 'old way' of waiting for clotting results before administering FFP.

Complications of transfusion

Blood transfusion after trauma is associated with adverse events, including increased mortality, postoperative infection, MOF, and sepsis. FFP and platelets have been implicated in increased rates of adult respiratory distress syndrome (ARDS), although, in contrast, early administration may be protective. It is imperative therefore to ensure correct delivery of appropriate blood products on an individualized basis.

Goal-directed therapy

Since the administration of blood products is associated with increased morbidity, and the exact ratio of protocol-driven resuscitation is unclear, it is imperative for the clinician to think about each blood product transfusion as soon as is reasonable during the resuscitation. The timing of this switch from protocol to targeted therapy depends on clinical circumstances, numbers of experienced personnel, and information available to the clinician.

Clotting tests should be performed to guide and monitor therapy: however, traditional laboratory tests take too long and their use in trauma has been challenged.[3] Platelet counts are rapidly available as long as the lab systems in a particular hospital are set up to perform the analysis immediately. Point-of-care (POC) arterial blood gas monitoring is rapid and gives information about base deficit and haemoglobin, but no information on coagulation status.

The use of thromboelastometry (TEG or ROTEM®) has been increasing during surgery and trauma. It is more likely to give a dynamic interpretation of whole blood clotting and monitor clot initiation, strength, fibrinolysis, and the relative contributions of functional fibrinogen and platelets. However, its use in trauma has not been validated and its benefits in guiding transfusion support and detecting fibrinolysis in trauma have not been fully elucidated. This view is not held in some European centres, where ROTEM® use to target coagulation therapy with fibrinogen and packed cell concentrates has led to a reduction in blood product usage with no reported adverse mortality rates. Schöchl and colleagues[8] found that by using ROTEM

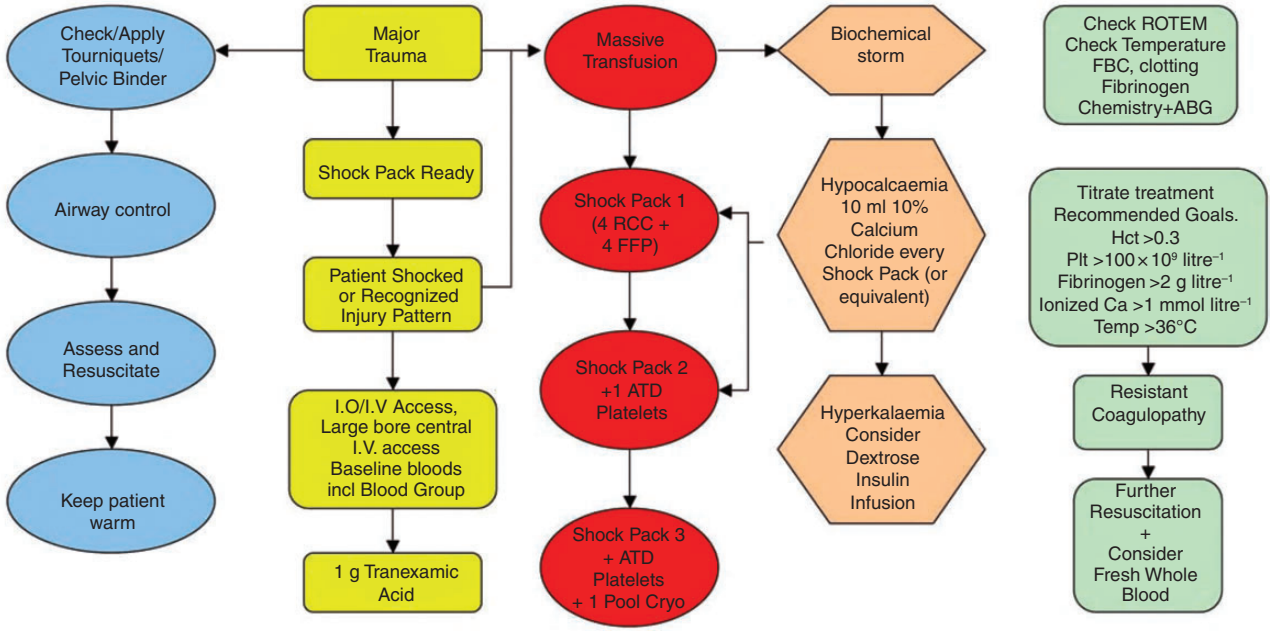

Fig 1 Guideline for the transfusion management of major ballistic trauma.

to guide therapy with fibrinogen concentrate as first-line haemostatic therapy in addition to prothrombin complex concentrate, a favourable survival rate was observed (14% *vs* 27.8%).

If clinicians are to effectively treat TIC, then effective monitoring of coagulation status must occur. In the absence of POC testing, robust mechanisms to expedite testing and disseminate lab tests must occur, especially in major trauma centres.

Practicalities of transfusion

Ensuring safe blood transfusion in a high stress trauma situation is extremely challenging. The right patient must get the right blood product. Local policies regarding better transfusion techniques must be rigorously adhered to. Half of the adverse events reported in 2011 to the UK database for tracking blood transfusion-related incidents, serious hazards of transfusion were due to human error.

In Camp Bastion hospital, Afghanistan, two trauma team members are allocated to setting up the transfusion in the trauma bay. They remain with the patient and are responsible for transfusion throughout the whole resuscitative surgery. This may not be practical in NHS hospitals where less staff are available; however, the advantages are that the team members who set up the transfusion are responsible for checking, administering, and recording all products transfused according to the clinicians instructions minimizing the chance for error. As their sole job is to deliver the transfusion, they are not distracted by other tasks. Since they know exactly what has been transfused, they are able to use their checklists to prompt the clinicians to take blood tests, prescribe platelets or cryoprecipitate, and maintain adherence to transfusion protocols.

Fluid challenges are given in 250 ml boluses once directed by the anaesthetist, administered via a warming rapid infuser device. The anaesthetist will direct the nurses as to what blood product to give, depending on lab and ROTEM® results, and set any other parameters (e.g. systolic AP) at which the nurses will prompt a request for further instructions. The nurses can also prompt the anaesthetist to request further blood product if available products are getting low.

Systemic treatments

Rapid administration of large quantities of stored blood will result in profound metabolic disturbance, the most significant of which are hyperkalaemia and hypocalcaemia. Hyperkalaemia should be monitored using ABG and treated with insulin and dextrose. Hypocalcaemia results from chelation of calcium by the citrate in stored blood. Calcium levels should be maintained above 1.0 mmol litre^{-1} by the administration of i.v. calcium using 10% calcium chloride or calcium gluconate. In the early stages of resuscitation, potassium and calcium monitoring may need to occur as often as every 15 min depending on the rate of blood product administration. Buffers are avoided where possible since they will mask the reversal of base deficit and or lactate as an indicator of adequacy of resuscitation.

The use of TXA has increased over recent years following the CRASH-2 trial.[9] This is one of the very few level 1 evidence trials in trauma and randomized more than 20 000 patients. CRASH-2 reported a reduction in overall mortality, especially if TXA was administered early. Of note, the follow-up paper reported an increased mortality if it was given after 3 h from the point of injury, the exact mechanism for this remaining unclear. Military data in the

MATTERS trial[10] supported the use of TXA demonstrating reduced mortality, especially after 24 h. Why the effect of TXA should occur late is not clear, but it is speculated that TXA may not only act on the acute bleeding/fibrinolytic stage, but also have an anti-inflammatory effect offsetting the effects of plasmin on the endothelium and white cells. It should be noted that the use of TXA has not been widely taken up in North America due to scepticism over trials conducted outside the North American trauma system and concerns over its prothrombotic effects. Further CRASH-2 analysis suggests that there is no increase in thrombotic events, and in fact there may even be a reduction in arterial thrombotic events. It is the authors' view that TXA should be given in a bleeding trauma patient according to CRASH-2 guidelines. This will be discussed in depth in another article to be published at a later date in *CEACCP* (Reed R, Woolley T. Uses of tranexamic acid. Accepted for publication.)

The use of recombinant activated factor VII (rFVIIa) is contentious as there is a risk of promoting unwanted thrombosis and it is not licensed for use in trauma. A multicentre randomized controlled trial examined the efficacy of rFVIIa, and found that treatment with rFVIIa in blunt trauma produced a significant reduction in massive transfusion requirement in patients surviving for more than 48 h, and reduced the incidence of ARDS. However, a Cochrane review recently concluded that the use of rFVIIa as a haemostatic drug remains unproven, so it is no longer recommended. rVIIa works by increasing thrombin generation from activated platelets, however, with HR, it seems likely that there are sufficient clotting factors in the blood stream and so thrombin generation is sufficient. The balance of risk therefore does not favour the use of rVIIa in a hospital with a well-supported transfusion system.

Treatment strategies

Pre-hospital management

Pre-hospital management of the bleeding patient should concentrate on stopping compressible haemorrhage and rapid evacuation to a trauma hospital where definitive treatment can occur. In a resource-limited environment, providers should follow ATLS recommendations of sequential airway, breathing, and circulation management (ABC); however, the military and other pre-hospital organizations have adopted a <C> ABC approach where catastrophic haemorrhage takes priority over airway management. First, responders should apply immediate compression and elevation to external wounds to reduce volume loss. A variety of topical haemostatic agents are now available, including mucoadhesive agents such as Chitosan (Celox) and factor concentrators like zeolite (QuikClot) that can be administered as prepared bandages, gauzes, swabs, or granules. These can be particularly useful for junctional haemorrhage in the groin or axilla. Tourniquets should be applied to uncontrolled limb haemorrhage. Early immobilization of long bone fractures and pelvic splints can also reduce blood loss. With continued haemorrhage, TXA should be considered. Some pre-hospital services are now able to commence blood product resuscitation before arrival in hospital, including the Medical Emergency Response Team (MERT) in Afghanistan and London Helicopter Emergency Service (HEMS), but this is not widespread across all pre-hospital services.

AP as a surrogate marker of blood flow is not a good endpoint after trauma due to the massive sympathetic tone and compensatory effects after volume loss. However, in a pre-hospital environment, it is still useful to resuscitate until a radial pulse is palpable, thereby limiting large increases in AP and causing further bleeding, while minimizing potential prolonged and irreversible hypoperfusion to the vital organs. During prolonged pre-hospital phases (over an hour), the UK military has adopted the concept of novel hybrid resuscitation where the AP is returned to normal after 60 min using whatever fluid is available (normally crystalloid) in order to limit the ongoing tissue hypoperfusion.

In-hospital management

In-hospital management should be a seamless continuation of pre-hospital management. The <C>ABC paradigm should be followed with concurrent activity by well-rehearsed teams. Tourniquets and compression bandages should be checked, if appropriate, and consideration given to changing to pneumatic tourniquets. Evidence of shock or incompressible haemorrhage should trigger an immediate response of surgery or interventional radiology with or without a CT scan on the way to the operating theatre. Fluid responders should still be treated with immediate/urgent surgery and rapid transfer considered without the need for full invasive monitoring or a completed secondary survey.

Administration of blood products should be guided by POC haematological results where possible. However, if the situation is evolving rapidly, or the patient too sick, product administration should follow predetermined MHP. It is imperative to target therapy as soon as possible and individualize the MHP at the earliest opportunity to limit inappropriate blood product transfusion.

The use of AP as a target should be used with caution since there can be significant hypovolaemia with normal AP due to compensatory mechanisms. This is especially true in the younger patient. Markers of hypoperfusion such as base deficit or lactate should guide therapy; however, these too have their limitations. In the absence of head injury, vasopressors should be used with caution in trauma since increases in vasomotor tone will further exacerbate the endothelial hypoxia in the microcirculation. There is some evidence that the use of vasopressors in trauma leads to worse outcomes. The presence of a head injury complicates this picture and maintenance of cerebral perfusion pressure should be prioritized over the avoidance of vasopressors.

The military have recently introduced an adaptation of the World Health Organization checklist consisting of a Command Huddle (carried out in the ED), Snap Brief, and situation reports to coordinate team management of the trauma patient. During the Command Huddle, a decision is made for immediate damage control surgery, for haemorrhage control, imaging, or ward management. Once in theatre, the Snap Brief is conducted to communicate the surgical

plan, blood products administered including rate, and any coagulopathy present. At 10 min intervals, updates are communicated as to time duration, blood products given, rate of infusion, clotting status and temperature with ROTEM®, and blood gas results and the surgical progress.

Conclusion

Resuscitation after haemorrhagic shock must deal with the insult resulting from the trauma itself, the insult from surgery, and the insult from treatment. It is the clinicians' responsibility to individualize therapy as early as possible to limit iatrogenic damage. Therapy should be targeted at resuscitating the microcirculation in order to reduce the inflammatory response while at the same time not allowing the lethal triad of hypothermia, coagulopathy, and acidosis to occur. The more aggressive use of targeted blood products seems to be beneficial in this respect, but the exact way in which to do this is the focus of much research and debate and remains unclear. It is likely that local policies enacted by well practised, well-rehearsed multidisciplinary teams will have a bigger impact on the success of a resuscitation than worrying about the correct ratios.

Declaration of interest

None declared.

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Please see multiple choice questions 1–4.