Battlefield resuscitation

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Current Opinion in Critical Care 2009, 15:527–535

Purpose of review

To bring together in one review article, the most current and relevant evidence relating to military trauma resuscitation.

Recent findings

The main themes highlighted by this review are coagulopathy of trauma shock (CoTS), damage control resuscitation, haemostatic resuscitation, the management of massive transfusion, use of adjuvant drugs for haemostasis and use of an empiric massive transfusion protocol.

Summary

The review aims to educate the readership in recent advances in trauma practice, culminating in a novel empiric massive transfusion algorithm seamlessly guiding the clinician through the initial resuscitation stage resulting in reduced mortality, morbidity, coagulopathy and decreased overall blood product usage.

Keywords

algorithm, damage control resuscitation, massive transfusion, trauma

Curr Opin Crit Care 15:527–535

1070-5295

Introduction

Battlefield resuscitation of major haemorrhage remains the highest priority of the defence medical services [1,2] and is the leading cause of preventable mortality in combat troops. Much work has been done on the design, implementation and evaluation of civilian trauma systems in the United States [3–6] and more recently, military trauma systems in the wake of the injuries sustained during the Iraq and Afghanistan conflicts [7–12]. The key to battlefield resuscitation is providing a seamless transition of care and much effort has gone into improving the care given by our Combat Medical Technicians (CMTs) at the point of wounding onwards. Our trauma system comprises four levels of care and is threat-related through care under fire, tactical field care, field resuscitation and finally advanced resuscitation. We instruct our own version of the Advanced Trauma Life Support course termed Battlefield Advanced Trauma Life Support (BATLS). This concentrates on treating catastrophic haemorrhage first. It then follows with airway, breathing and circulation. Some of the variations from ATLS include the use of physician-led prehospital retrieval delivering rapid sequence intubation (RSI), blood products, thoracotomy, hypotensive resuscitation, tourniquets and advanced haemostatic dressings.

The concepts of damage control resuscitation (DCR) [13] and damage control surgery (DCS) [14,15] are terms well recognized in military and civilian trauma medicine. Haemostatic resuscitation is defined as the rapid and proactive treatment of the coagulopathy associated with major injury [16]. Key to understanding the concept of haemostatic resuscitation is unravelling the mysteries surrounding acute coagulopathy of trauma shock (ACoTS). Aggressive treatment of the 'lethal triad' of hypothermia, acidosis and coagulopathy is now recognized as pivotal in improving outcome. Recent work has introduced the concept that hypoperfusion, hyperfibrinolysis, activation of protein C and up-regulation of thrombomodulin pathways contribute to ACoTS [17,18••].

During a recent and very busy military tour of Afghanistan (June–Oct 2008) we attempted to combine the latest evidence regarding massive transfusion and the management strategies targeting hypoperfusion, hyperfibrinolysis, acidosis, hypothermia and ACoT pathophysiology into a single flowchart based algorithm for use in the prehospital phase, emergency department (ED), operating theatre and intensive care unit (ICU). We termed the combination of blood products and other damage control measures 'damage control shock resuscitation (DCSR)'. The initiation trigger for DCSR was the requirement for more than 5 units of packed red blood cells (PRBCs).

Anaesthetic management and the medical emergency response team

An integral part of the British Military Trauma System is the medical emergency response team (MERT). The team comprises an attending physician (anaesthesiologist or emergency medicine), paramedic and nurse. This

helicopter (CH-47) team aims to project critical care forward and initiate advanced resuscitation techniques early and as close to the point of wounding as possible. As well as advanced resuscitation equipment, it carries PRBCs, fresh frozen plasma (FFP) and the facility to warm these products.

Rapid sequence intubation

If not already intubated, the anaesthetist on MERT or at the field hospital will assess the airway and undertake an RSI if necessary. The choice of induction agent is often a contentious one [19–21]. Our practice in hypovolaemic shocked patients (i.e. no radial pulses or systolic blood pressure <90 mmHg) is to use one-tenth to one-half of the normal dose of sodium thiopentone (STP). In shocked acidotic patients, STP becomes increasingly unionized, hence smaller doses are required to achieve the same end point. STP has the advantage of rapid onset, no adrenal suppression or sympathomimetic action and is rapidly distributed. Subsequent tachycardia or hypotension postintubation should therefore be attributed to ongoing hypovolaemia. Ketamine should also be considered at a dose of 1–2 mg/kg (racemic) in shocked head-injured patients [22,23], as any single reduction in mean arterial pressure (MAP) below 90 mmHg confers a doubling of mortality with subsequent drops additive [24–26]. Suxamethonium at a minimum dose of 1.5 mg/kg should be given for RSI [27–30], unless there is a contraindication where rocuronium at a dose of 1.2 mg/kg is our choice [31–34].

Intubation

The use of a size 8-mm internal diameter cuffed oral endotracheal tracheal tube for all adult patients preprimed with either a long endotracheal introducer or a stylet reduces the time to intubation. Current evidence favours the long endotracheal introducer [35]. The use of a size 4 Macintosh laryngoscope blade in adult patients is also advised. The use of novel intubation devices such as Airtraq [36–38], Glidescope [39] and GlideRite endotracheal tubes [40,41] are useful adjuncts on the MERT, ED, operating theatres and ICU.

Venous access

During the primary survey, extensive injuries such as bilateral amputations and unstable vital signs will alert the MERT anaesthetist or trauma team that the patient may require massive transfusion. The priority following the primary survey and securing the airway is to obtain high flow capacity central venous access. This ideally should be above the diaphragm [42]. This avoids the potential complication of cannulating the femoral artery due to its close anatomical relation to the vein, its possible discontinuity with the heart, increased infection and thrombosis rates, and actually placing this large line in the milieu that exists at this time. A space usually exists between the surgeon and the patients' outstretched arm. We place a large bore central line (e.g. MAC or Swan Sheath; Arrow International) into the right subclavian vein which confers easier anatomical access and invariably remains patent even in hypovolaemia. If an intercostal drain has been placed in the left hemithorax, then it is prudent to place the central line on that side. The lines are often quick to insert in experienced hands. Sterility is important and it is our practice to change all lines in the ICU.

Transfusion management

There are many definitions of massive transfusion, most commonly transfusion of more than 10 units of PRBCs in 24 h. We also classify more than 4 units of PRBCs in 1 h as an alternative definition. Early identification of those patients requiring massive transfusion is inevitably the first and most important step in this algorithm. Work on civilian scoring systems aiming to triage patients from site of injury to the most appropriate facility have been undertaken since the Vietnam war and have been discussed previously. Few, however, have focussed on identifying those in the field that may require massive transfusion at the receiving facility [43•,44]. Administration of blood products often begins in flight, but when not available, the MERT doctor will alert the field hospital that the patient may require a massive transfusion. The decision to initiate the protocol is often made before arrival at the field hospital.

Shock packs

The provision of 'shock packs' has changed significantly how we manage DCSR. These packs consist of 4 units of thawed FFP and 4 units of PRBCs. One platelet apheresis pool is made available. This avoids the logistical delay with the laboratory. DCSR can thus start immediately and avoids the use of 'filler fluids' (crystalloids).

Packed red blood cells, fresh frozen plasma, platelets and cyroprecipitate

The high prevalence and profound impact of coagulopathy mandates timely treatment. The currently available coagulation tests of prothrombin time and activated partial thromboplastin time are not sufficiently sensitive to guide blood product use in trauma patients [45]. The tests bear little relation to coagulation *in vivo*, and neglect the contribution of platelets or temperature. The length of time to undertake is also an issue [46•]. The decision to institute clotting factor replacement therefore becomes empiric. The aggressive early administration of FFP to

attenuate the coagulopathy of trauma was pioneered during the recent conflicts in Iraq and Afghanistan, and current American and British military practice is to administer warmed FFP and PRBCs in a 1 : 1 ratio as soon as possible [13,47]. In one large retrospective analysis of 246 military patients who received a massive transfusion of 1 : 1 PRBC to FFP, mortality rate was reduced by 60% in comparison to a ratio of 1 : 8 [48]. Although the evidence for these strategies is still emerging, other civilian trauma centres are now producing similar results [49,50,51•]. Our practice was to modify this ratio by further adding platelets, resulting in a ratio of 1 : 1 : 1 PRBC : FFP : platelets [52]. One adult pool of platelets yields an effective concentration of only 30–40×10^9 platelets. Using platelet apheresis in theatre, which yields 3–5 adult pools, we gave 1 platelet pool every 5 'units' of 1 : 1 PRBC to FFP achieving a 1 : 1 : 1 ratio. Current guidelines have recommended maintaining a level of $>100 \times 10^9$ platelets in polytrauma [53–55]. Fibrinogen concentration is also important in establishing haemostasis [56], and we administered 1 unit of cryoprecipitate every 10 PRBCs which maintained a fibrinogen level greater than 1.0 g/l. An area of concern is PRBC age. A recent large retrospective analysis of blood usage in one trauma centre found when patients required more than 5 units of blood, administering more than 3 units of PRBC older than 14 days effectively doubled their mortality [57]. It is our practice only to give blood less than 14 days old to patients requiring more than 5 units.

Warm fresh whole blood

Warm fresh whole blood (WFWB) has been used in every military conflict since the first World War. This practice in civilian hospitals ceased after component therapy became common in the early 1980s [58–61]. However, it is still used today by the military for logistical reasons, and its ability to treat coagulopathy resistant to conventional therapy [62]. We utilized WFWB in the ICU for persistent and resistant postoperative coagulopathy with good results. Two recent reviews have concurred with our findings [63,64]. One disadvantage is the speed in obtaining WFWB, as finding donors requires time. There remains an inherent risk of nonscreened virus transmission [65].

Antifibrinolytics

Hyperfibrinolysis is common after trauma and is a direct consequence of both tissue injury and shock due to the activation of protein C and the thrombomodulin pathway [18••]. Tranexamic acid is a synthetic lysine analogue and a competitive inhibitor of plasmin and plasminogen. In a dose of 15 mg/kg it has been shown to reduce blood loss in elective surgical patients by inhibiting fibrinolysis [66]. A systematic review of randomized controlled trials involving antifibrinolytic agents showed they reduced blood transfusion by a third, the volume transfused by one unit and halved the need for further surgery due to haemorrhage in elective surgical patients [67,68]. The efficacy of tranexamic acid in trauma is currently being assessed by the CRASH II study (Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage), in which 20 000 trauma patients worldwide are being randomly assigned to 1 g of tranexamic acid followed by 1 g infused over 8 h [69]. Use of tranexamic acid was recommended in the European Guideline on Management of Bleeding in Trauma in 2007 [27]. Our practice was to administer 15 mg/kg of tranexamic acid as soon as transfusion commenced then repeat every 10 units of PRBCs.

The role of recombinant activated factor VII

Factor VII is a crucial component of coagulation, binding to tissue factor – a lipoprotein present in endothelial cells – exposed by injury, thus generating factor Xa and subsequently thrombin. Recombinant activated factor VII (rFVIIa) is licensed for use in patients with haemophilia and inhibitory antibodies. Its local enhancement of haemostasis at the site of injury has stimulated research into possible uses in trauma [70–72]. Two parallel, multicentre, randomized controlled trials have shown a statistically significant reduction in blood transfusion requirements in blunt (not penetrating) trauma patients treated with rFVIIa [73]. Although the trial and statistics have been the subject of criticism, these studies remain some of the best evidence available to us. The effectiveness of rFVIIa (not limited to trauma) has also been assessed by a Cochrane review, but concluded that rFVIIa as a haemostatic drug remains unproven [74]. Although not licensed for the treatment of traumatic haemorrhage, the use of rFVIIa continues. Given its substantial cost, further research is warranted. Previously, it has been our policy to give rFVIIa after six PRBCs to any salvageable patient with continuing haemorrhage that has failed surgical and nonsurgical methods. However, with the advent of DCSR we find that patients are now less coagulopathic, acidotic or hypothermic. Our use of rFVIIa has therefore declined considerably.

When administering rFVIIa we concurrently administer a unit of FFP, cryoprecipitate and platelets. By combining rVIIa with fibrinogen, platelets and clotting factors we postulate we are providing all of the factors necessary to produce an effective clot. This combination we have affectionately named 'Bastion glue' after the field hospital in Helmand, Afghanistan.

Permissive hypotension

'Hypotensive' resuscitation is our standard practice in haemorrhaging patients without traumatic brain injury

[75]. Numerous animal models of uncontrolled haemorrhagic shock have demonstrated improved outcomes when a lower than normal mean arterial pressure (MAP) of 60–70 mmHg is taken as the target for fluid administration during active haemorrhage [76]. Course doctrine from the UK BATLS course is to initially resuscitate to a palpable radial pulse [77••]. Hypotension facilitates in-vivo coagulation, whereas the avoidance of bolus doses of crystalloid fluid both preserves normothermia and prevents excessive dilution of PRBCs, platelets and clotting factors. Two large human trials have demonstrated the safety of this approach relative to the conventional target of greater than 100 mmHg, suggesting various benefits including shorter duration of haemorrhage and reduced mortality [78,79]. It is our practice to resuscitate to a systolic blood pressure (SBP) of no more than 90 mmHg. In tandem with 1 : 1 : 1 PRBCs : FFP : platelets, this SBP target often achieves an optimum haematocrit (Hct) of around 0.3. This Hct level has been postulated as the minimum level necessary to ensure enough 'shear stress' within a blood vessel to force platelets to the periphery to form primary haemostatic plugs and initiate coagulation.

The role of calcium

Hypocalcaemia is common in critically ill patients and is associated with increased mortality [80]. Hypocalcaemia is known to cause cardiac effects [81] and is heavily involved in the coagulation process [82]. A reduction in calcium levels also causes a reduction in platelet activity [83]. Citrate is frequently used in blood products as an anticoagulant and is a very effective scavenger of calcium. FFP particularly has excess levels of citrate. This in turn causes a drop in free calcium concentration [84,85].

In a recent review article on preconditions for haemostasis, recommendation was made to maintain ionized calcium concentrations above 0.9 mmol/l [78] but it is our practice to maintain ionized calcium above 1 mmol/l. It is worth noting that there are different preparations of calcium. 1 ml of calcium gluconate 10% contains only 226 micromols of calcium, whereas the same volume of calcium chloride 10% contains 680 micromols [86].

Hyperkalaemia

Although others had experienced hyperkalaemia during massive transfusion which sometimes proved fatal [87], we had little experience from previous deployments. During this deployment, however, hyperkalaemia became a common finding during resuscitation with one case of refractory hyperkalaemia. We postulated a number of mechanisms, such as advancing age of PRBCs, cell lysis through high flow pressure infusors, muscle damage from trauma, and the possibility that as this was a summer operational tour, undertaking a high degree of physical work, soldiers may have become progressively chronically dehydrated or even a consequence of blast injury. We hypothesized that hypoperfusion may have existed before trauma, contributing to potassium release as the patient progressively vasodilated during resuscitation. Our treatment involved standard care: calcium to protect the myocardium and an insulin/dextrose combination which rapidly gained control in all but one patient.

Temperature control and hypothermia

Coagulation disorders are temperature-dependent and related to enzyme dysfunction, platelet dysfunction, and increased fibrinolytic activity [88]. Coagulation cascade enzyme reactions are strongly inhibited by hypothermia [89]. In one study, a temperature of 34°C was the critical point at which enzyme activity in trauma patients slowed significantly, and at which significant alteration in platelet activity was observed [90]. Recommendations are to maintain a temperature of at least more than 34°C [86] or even 36°C [90]. Despite the presence of normal clotting factor levels, at temperatures below 33°C, hypothermia produces a coagulopathy that is equivalent to 50% of normal activity at normothermia [91]. In summary, between 37 and 33°C, haemostatic defects primarily result from a defect in platelet adhesion and aggregation, and below 33°C, dysfunctional enzymatic activity. The net result of hypothermia is coagulopathy. It must be noted that even the isolated and superficial cooling of a limb with preserved core temperature results in a much prolonged bleeding time.

The avoidance and correction of hypothermia appears critical in preventing or correcting coagulopathy in a patient receiving massive transfusion. Therefore, the appropriate treatment for purely hypothermia-induced coagulopathy is warming rather than giving clotting factors. Hypothermia must be managed with a 360° approach as recommended by the UK National Institute for Health and Clinical Evidence (NICE) [92]. Heat loss during the resuscitation phase is primarily caused by administering cold fluids and is proportional to amount given and the temperature difference between the patient and the fluid [93]. The energy needed by the body to warm 2 l of fluid infused at 25°C within 1 h exceeds the energy that can be delivered by conventional warming methods in the same time [94]. As discussed previously we initially resuscitate patients to a systolic pressure of 90 mmHg and keep prehospital cold fluid administration to a minimum. The resuscitation room and the operating theatre must be warmed. All fluids administered must pass through a warmer. Hot air convection should be used and the patient insulated as much as possible, which can be difficult when large surgical

exposure is required. In the authors' experience under patient heated mattresses are essential in maintaining patient temperature above 36°C in this instance.

Metabolic acidosis

Virtually all coagulation stages are inhibited by acidosis. Platelets alter shape at a pH below 7.4 [95], Ca^{++} binding sites are pH-dependant, but the main process inhibited is thrombin generation [65]. Unsurprisingly, trauma non-survivors are more likely to have a lower pH than survivors [96]. Martini *et al.* [97] demonstrated that thrombin generation was inhibited by a pH of 7.1 by as much as 50% with an additional 35% reduction in fibrinogen. Platelet count was also reduced by 50% [97].

In addition to pH, base deficit is a sensitive indicator of hypoperfusion [98], correlates with mortality [99] and at levels below −12.5 has been demonstrated to directly inhibit coagulation [100,101]. It has also been used to predict transfusion requirements [102].

A recent excellent review concluded that a notable impairment of haemostasis arises at pH 7.1 and below, with similar effects observed at base deficit of −12.5 or less [103••]. Thus, when there is severe haemorrhage and acidaemia, buffering toward physiologic pH values is advantageous, especially when massive transfusions of older PRBCs displaying exhausted red blood cell buffer systems are used [90].

Tris-hydroxymethyl aminomethane (THAM) is a biologically inert amino alcohol of low toxicity. *In vivo*, THAM supplements the buffering capacity of the blood bicarbonate system, accepting a proton, generating bicarbonate and decreasing the partial pressure of carbon dioxide in arterial blood. It rapidly distributes through the extracellular space, slowly penetrates the intracellular space and is excreted by the kidney. Unlike bicarbonate, which requires an open system for carbon dioxide elimination to exert its buffering effect, THAM is effective in both closed and semi-closed systems, and maintains its buffering power even in the presence of hypothermia [104]. Minute volume ventilation does not alter with THAM, unlike bicarbonate, when the minute volume can increase by as much as 40% [105]. Administration of sodium bicarbonate may also inhibit the conversion of fibrinogen to fibrin [106], whereas THAM may not affect thrombin generation [107]. Hypoperfusion is cited as significant contributor to ACoTS [18••] and a further anaesthetic refinement we initiated was the use of high-dose fentanyl as used widely during cardiothoracic anaesthesia. In conjunction with a low concentration volatile agent (typically isoflurane at a minimum alveolar concentration of no more than 0.4–0.5) fentanyl facilitated a high degree of vasodilation, but with excellent analgesia and anaesthesia, promoting 'washout' from previously hypoperfused areas. We promoted a 'flow not pressure' doctrine. This in turn reduced base deficit, increased lactate clearance and we postulated ceased the vicious cycle of CoTS as it promotes peripheral perfusion and washout.

The use of vasopressors in haemorrhagic shock

A recent multicentre prospective cohort study in blunt trauma patients in haemorrhagic shock demonstrated a two-fold increase in mortality associated with the use of vasoconstrictors when compared to treating with aggressive fluid resuscitation [108]. We steadfastly avoided any use of vasopressors and simply administered blood products until the SBP reached 90 mmHg. We found that this avoids unexpected shock and increased our ability to clear base deficit quickly. We resisted the temptation to place arterial lines until this target was reached as experience taught us that it is often futile, causes needless arterial trauma and distracts the physician from resuscitation.

Algorithm

Our algorithm for the management of major haemorrhage is presented in Fig. 1. It consists of a central 'core' of major management steps considered sequentially in red. Further management steps arising from decisions from the central core are set out on the left in blue. Information and advice boxes in orange are to the right and left of the central core. The flowchart is easy to follow and gives what we feel is the most current evidence based management of massive transfusion in military medicine at present.

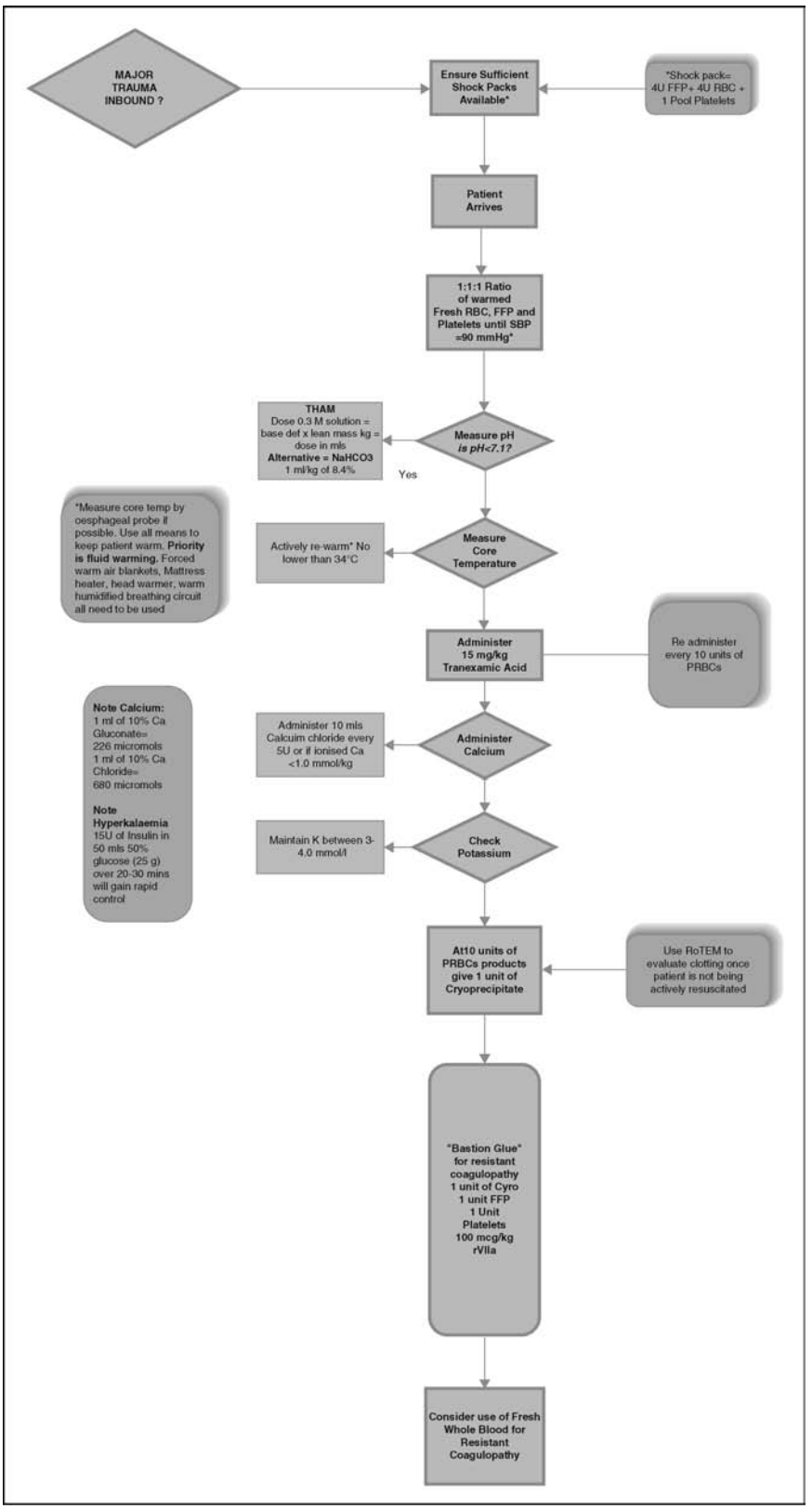
Conclusion

In military medicine, trauma resuscitation is rapidly becoming a specialty in its own right and involves mastering several different skill sets. Leadership, a high degree of technical ability and a sound knowledge base are all essential. Any chain is only as strong as its weakest link but we must strive to ensure that all links in our 'chain of survival' are at least present.

Unfortunately, we are acquiring a huge amount of experience in resuscitation and constantly updating and refining our techniques. Patient survival continues to improve despite the ever increasing ingenuity and lethality of the enemies' weapons. Promulgation of new techniques and knowledge to colleagues becomes ever more important in this ever changing field.

The future of trauma management has several exciting developments. We, like others, are currently evaluating

Figure 1 Major transfusion algorithm



Algorithm: Our algorithm for the management of major haemorrhage is presented above. It consists of a central 'core' of major management steps considered sequentially in red. Further management steps arising from decisions from the central core are set out on the left in blue. Information and advice boxes in orange are to the right and left of the central core. The flowchart is easy to follow and gives what we feel is the most current evidence based management of massive transfusion in military medicine at present.

the use of thrombo-elastography in managing coagulopathy of trauma [109,110]. It is already changing our practice and allows us to target therapy in the nonacute resuscitation stage. Previous work focused on guiding blood product use in cardiothoracic anaesthesia [111].

Other work has looked at the use of recombinant erythropoietin (rEPO) during the critical care phase. rEPO has demonstrated a survival advantage in two critically ill patient cohorts in prospective, randomized clinical trials, which were not affected by baseline factors including trauma-specific variables [112]. However, the use of rEPO in resuscitation or during surgery has not yet been studied.

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- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 601).

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