

## Damage control resuscitation for patients with major trauma

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Military conflict has always driven innovation and technical advances in medicine and surgery. Accepted concepts of trauma resuscitation and surgery have been challenged in the wars in Iraq and Afghanistan, and novel approaches have been developed to address the current complexity and severity of military trauma.<sup>1</sup> A number of these new strategies have evolved into a single seamless approach that extends from the point of wounding to surgery, and on to critical care. Although the precise contribution of medical care is difficult to ascertain, better trauma management has almost certainly contributed to a remarkable reduction in the lethality of war wounds. Only 10% of United States servicemen wounded in Iraq and Afghanistan between 2003 and 2009 died, compared with 24% in the first Gulf War (1990-1991) and Vietnam War (1961-1973).<sup>w1</sup> Initially derived from clinical experience, new concepts in caring for the injured have been refined with experiment and study and have been translated back to the battlefield in a dynamic process.<sup>2</sup> Many of these advances are also relevant to trauma care in civilian practice. The aim of this article is to provide an overview of a new approach to managing major trauma known as “damage control resuscitation”, which is applicable to trauma casualties most at risk of traumatic coagulopathy and death, and aims to address all aspects of the “lethal triad” immediately on receiving the injured patient.<sup>2</sup>

### What is the “lethal triad”?

The term “lethal triad” is used to describe the mutually perpetuating combination of acute coagulopathy, hypothermia, and acidosis seen in exsanguinating

trauma patients (fig 1). Hypoperfusion leads to decreased oxygen delivery, a switch to anaerobic metabolism, lactate production, and metabolic acidosis. Anaerobic metabolism limits endogenous heat production, exacerbating hypothermia caused by exposure and injudicious administration of cold resuscitation fluids and blood. Large, well conducted retrospective studies have shown that a core temperature of less than 35°C on admission is an independent predictor of mortality after major trauma.<sup>3w2</sup>

Several observational studies have shown that around a quarter of trauma patients have an established, early coagulopathy on arrival in the emergency department, a finding associated with a four fold increase in mortality.<sup>4-6</sup> Coagulopathy was classically considered to be the product of procoagulant protease losses (a result of consumption and bleeding), dilution (due to fluid resuscitation), and dysfunction (related to acidosis and hypothermia). Recent research, however, has shown that the pathophysiology of coagulopathy is more complex.<sup>7-9</sup> Two prospective observational studies have shown that hypoperfusion is an important driver of early post-injury coagulopathy, although tissue injury is the initiating event. In addition, both anticoagulation and hyperfibrinolysis appear to contribute to coagulopathy.<sup>7,8</sup> The resulting haemostatic derangement is distinct from disseminated intravascular coagulation and has been termed acute coagulopathy of trauma-shock.<sup>9</sup> An understanding of these underlying mechanisms forms the basis of haemostatic resuscitation.

### What are the new strategies in trauma resuscitation?

Damage control resuscitation combines two seemingly diverse strategies—permissive hypotension and haemostatic resuscitation—with damage control surgery (fig 2).<sup>2 w3 w4</sup> The foundation for this approach is set in the pre-hospital environment, where intravenous fluid administration is restricted to a volume sufficient to maintain a radial pulse.<sup>w3</sup> The term “haemostatic resuscitation” describes the very early use of blood and blood products as primary resuscitation fluids, to treat intrinsic acute traumatic coagulopathy and to prevent the development of dilutional coagulopathy.<sup>2,4</sup> Tranexamic acid, recombinant factor VIIa, and short

### Sources and selection criteria

We searched the Embase database, the Medline database, and the Cochrane library for observational studies, trials, and systematic reviews. In our search, we used combinations of the following search terms: trauma; wounds and injuries; damage control; resuscitation; permissive hypotension; recombinant factor VIIa; tris(hydroxymethyl) aminomethane; tranexamic acid; and hypothermia. We also performed open internet searches. We then manually cross referenced the reference lists of articles to expand our search results. Some of the studies identified are of poor quality, reflecting the difficulties of conducting high quality research in trauma care.

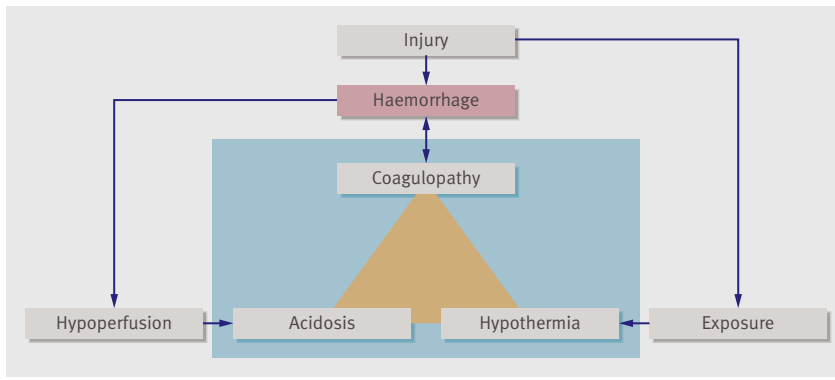


Fig 1 | The “lethal triad” of acidosis, hypothermia, and coagulopathy

term administration of tris(hydroxymethyl)amino-methane can also be used to “buy time”.

Damage control resuscitation is designed to proceed hand in hand with damage control surgery. The sequential strategy of operation followed by resuscitation has been replaced by an integrated approach so that resuscitation and surgery are undertaken simultaneously, with close communication and cooperation between surgeon and anaesthetist.

#### What is permissive hypotension?

During the second half of the 20th century, restoring normal circulatory function by aggressively replacing intravenous fluids was seen as pivotal in preventing haemorrhagic shock. Uncorrected haemorrhagic shock, the consequence of interrupted oxygen delivery as a result of blood loss, leads to cellular ischaemia, progressive organ dysfunction, and ultimately irreversible organ failure.

The recognition that fluid resuscitation might interfere with haemostatic mechanisms, ultimately exacerbating blood loss, led to a re-evaluation of this accepted approach. Permissive hypotension—also known as “hypotensive” or “balanced” resuscitation—is a strategy of deferring or restricting fluid administration until haemorrhage is controlled, while accepting a limited period of suboptimum end-organ perfusion.

Proving the usefulness and safety of such an approach is beset by practical difficulties. A large non-randomised trial conducted in the early 1990s showed a statistically significant 8% absolute reduction in mortality for hypotensive patients with penetrating torso trauma assigned to delayed (in the operating theatre) compared with pre-hospital or emergency room fluid

resuscitation.<sup>10</sup> Pre-hospital times were very short and patients in this study were mostly young; thus, extrapolating the findings to other settings or mechanisms of injury might not be appropriate. A cluster randomised trial of patients who had sustained mainly blunt trauma showed no difference in mortality between the delayed and immediate resuscitation groups, but included patients with relatively minor injuries and had many protocol violations, rendering the comparisons and conclusions meaningless.<sup>11</sup> A third, smaller randomised trial of patients with either blunt or penetrating hypotensive trauma also showed no difference in mortality between controlled fluid resuscitation and conventional treatment,<sup>12</sup> but again the study had considerable methodological shortcomings. These three trials were included in a Cochrane review—which also assessed two trials not pertaining to trauma patients—and a high quality systematic review, both of which showed no difference in mortality between early and delayed fluid administration.<sup>w5 w6</sup>

No published evidence exists to support the strategy of permissive or controlled hypotension, although its usefulness has not been entirely ruled out either. Few would argue against replacing lost intravascular volume in patients with controlled or self limiting haemorrhage. In patients with uncontrolled haemorrhage, particularly in the context of penetrating torso trauma, a strategy of permissive hypotension, together with expert resuscitation and rapid control of haemorrhage, might be more appropriate. It is conceivable that permissive hypotension is more applicable to the management of penetrating trauma, which is often characterised by the presence of major vascular injuries, than to blunt injuries.

Despite the lack of evidence, guideline recommendations for clinical practice point towards judicious administration of intravenous fluids. In recognition of the unique challenges posed by combat casualties, permissive hypotension has been incorporated into military medical doctrine<sup>2 13 w7</sup> and used widely during the recent conflicts in South West Asia. The National Institute for Health and Clinical Excellence has endorsed permissive hypotension in the civilian pre-hospital setting and advises against fluid administration in patients without head injury if a radial pulse is palpable.<sup>w8</sup> The forthcoming 8th edition of the Advanced Trauma Life Support programme also emphasises the need to balance the risk of precipitating further bleeding against the adequacy of organ perfusion by accepting a lower than normal blood pressure.<sup>w9</sup>

The management of polytrauma patients with head injuries requires special mention. The importance of maintaining cerebral perfusion pressure is well recognised; thus permissive hypotension is currently contraindicated in this setting.

#### What is haemostatic resuscitation and why perform it?

Although aggressive and simultaneous management of all three aspects of the “lethal triad” is important, rapid and proactive treatment of the coagulopathy associated with major injury is now recognised as central

#### Box 1 Hypothermia prevention and treatment strategies

- Limit casualties' exposure
- Warm all blood products and intravenous fluids before administration
- Use forced air warming devices, which are useful before and after surgery but are less effective when the need for operative exposure restricts application to the limbs
- Employ carbon polymer heating mattresses, which are highly effective and do not restrict surgical access, and are, therefore, the device of choice for the operating theatre

to improving outcome.<sup>13 14</sup> Strategies include: administration of fresh frozen plasma and platelets; use of recombinant factor VIIa, cryoprecipitate and tranexamic acid; and calcium replacement.

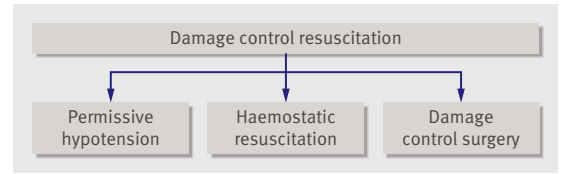
The high prevalence and profound impact of coagulopathy mandates timely treatment of trauma patients. Commonly available diagnostic tests—such as prothrombin time and activated partial thromboplastin time—are inappropriate for guiding treatment in trauma patients owing to their poor sensitivity and the delay in obtaining results,<sup>13 14</sup> so the decision to initiate clotting factor replacement is a clinical one.

**How much fresh frozen plasma should I give?**

In patients predicted to require massive transfusion, current US and British military practice is to administer fresh frozen plasma and packed red blood cells in a 1:1 ratio.<sup>2 14</sup> The aggressive and early administration of fresh frozen plasma to attenuate the acute coagulopathy of trauma shock was pioneered by military surgeons during the recent conflict in Iraq.<sup>15</sup> A small but well conducted retrospective analysis of military casualties who needed massive transfusion showed a statistically significant absolute reduction in mortality (46%) for those who had been resuscitated with fresh frozen plasma and packed red blood cells in a 1:1 ratio compared with a more conventional 1:8 ratio.<sup>15</sup> Similar subsequent civilian studies from the US and Germany, which incorporated both patients with penetrating trauma and those with blunt trauma, have produced broadly confirmatory results.<sup>16-20</sup> All these studies were, however, retrospective.

**When should I give platelets?**

Military guidelines for haemorrhagic shock also recommend the administration of platelets in a 1:1 ratio with packed red blood cells.<sup>2 14 15</sup> The administration of platelets and packed red blood cells in combination with a 1:1 ratio of fresh frozen plasma and packed red blood cells approximates giving whole blood. This approach is conceptually attractive but based on limited evidence. The effect of high platelet to packed cell ratios has only been investigated in two retrospective observational studies. Both studies showed improved survival with a 1:1 ratio compared with lower ratios.<sup>17 19</sup> More studies are needed before firm recommendations can be made but, in the meantime, administration of at least one pool of platelets (four to six



**Fig 2** | The components of damage control resuscitation

individual donor units) for every five units of packed red cells to trauma patients requiring massive transfusion seems reasonable.

**Is there a role for factor VIIa?**

Recognition of the importance of trauma related coagulopathy has prompted a search for pharmacological adjuncts to treatment. Recombinant factor VIIa is licensed for use in patients with haemophilia and inhibitory antibodies. Factor VII is a crucial initial component of the coagulation cascade. This agent is thought to enhance local haemostasis at the site of injury and is therefore being investigated for its possible uses in trauma management.

Two parallel, multicentre, randomised controlled trials of recombinant factor VIIa have shown a statistically significant reduction in blood transfusion requirements in patients with blunt, but not penetrating, trauma.<sup>21</sup> The design and statistical analysis of these trials have been the subject of criticism, but the studies represent the best available evidence. A Cochrane review not limited to trauma patients concluded that the effectiveness of recombinant factor VIIa as a general haemostatic drug is unproven.<sup>w10</sup> Although not licensed for the treatment of traumatic haemorrhage, the use of recombinant factor VIIa continues in practice. In view of the substantial cost of the product, further studies, in particular economic analyses, are needed. The widespread application of haemostatic resuscitation principles—in particular the early and targeted use of fresh frozen plasma and platelets—might lead to a decrease in the use of recombinant factor VIIa.

**When should I consider giving fibrinogen concentrate or cryoprecipitate?**

Fibrinogen deficiency develops earlier than deficiency of other clotting factors.<sup>14 w11</sup> Fibrinogen is, therefore, an obvious target for replacement with either cryoprecipitate—which contains fibrinogen, factor VIII, factor XIII, and von Willibrand factor—or fibrinogen concentrate. British and European guidelines recommend giving either product if plasma fibrinogen levels fall below 1.0 g/l.<sup>w11 w12</sup> Concerns about patient exposure to a large number of donors and the associated risk of blood borne virus transmission limit the use of cryoprecipitate to situations where conventional treatment has failed.

**Is there a place for tranexamic acid?**

Recognition of the contribution of hyperfibrinolysis to the development of acute coagulopathy in trauma shock has led to renewed interest in antifibrinolytics.

**Unanswered questions**

- Which patients would benefit the most from haemostatic resuscitation, and how should these patients be identified at the outset of resuscitation?
- What is the optimal ratio of fresh frozen plasma, packed red cells, and platelets?
- Which patients will benefit from permissive hypotension?
- What are the precise indications for recombinant factor VIIa, tranexamic acid, and cryoprecipitate?
- Would better resuscitation reduce the need for damage control surgery and allow more patients to undergo primary definitive repair?

**TIPS FOR NON-SPECIALISTS**

- Early identification of uncontrolled bleeding is essential; treatment requires surgical haemostasis rather than aggressive fluid administration
- In patients with haemorrhagic shock, early treatment with fresh frozen plasma and platelets in addition to packed red blood cells is initiated
- Hypothermia prevention should be initiated as early as possible using fluid warmers, forced air blankets, and warming mattresses

Although tranexamic acid has been shown to reduce blood loss after elective surgery,<sup>w13 w14</sup> no direct evidence of a beneficial effect in trauma patients is available. A recent Cochrane review identified only two applicable primary studies—comprising a total of only 90 patients—and concluded that the evidence was insufficient to support or refute a clinically important treatment effect.<sup>w15</sup> On the basis of extrapolated evidence from studies of elective surgery, and given the lack of serious adverse effects, European guidelines for the management of bleeding after major trauma recommend tranexamic acid as an adjunct to the management of traumatic haemorrhage.<sup>w12</sup> An ongoing, large, randomised, placebo controlled trial of the effect of tranexamic acid on mortality and on transfusion requirements in trauma patients is expected to provide higher level evidence.<sup>w16</sup>

**When should I give calcium?**

Ionised hypocalcaemia is common in critically ill patients and is associated with increased mortality.<sup>w17</sup> Calcium is an important cofactor to many components of the coagulation cascade. Citrate, used as an anticoagulant in many blood components, chelates calcium and exacerbates hypocalcaemia. The dose-response effect of hypocalcaemia on coagulation is difficult to measure.<sup>w18</sup> A recent non-systematic review, however, extrapolated that ionised calcium concentrations of less than 0.6-0.7 mmol/l could lead to coagulation defects and recommended maintaining a concentration of at least 0.9 mmol/l.<sup>w19</sup>

**Does the storage age of packed red blood cells matter?**

The transfusion of red cells with a high storage age has been associated with increased rates of infective complications and multiple organ failure.<sup>w20 w21</sup> Although the shelf life of packed red cell units is around six weeks, adverse effects of administration—which are thought to be mediated by passenger leukocytes—have been shown with units at a storage age of about two weeks.<sup>w20 w21</sup> A recent large retrospective cohort study of trauma patients showed that transfusion of red cells stored for longer than two weeks was associated with significantly increased odds of death. This finding was observed despite leukoreduction, but was apparent only among patients who received at least six units of packed cells.<sup>w22</sup> Recently donated red cells are, therefore, preferable for trauma patients requiring massive transfusion, although such a practice has obvious logistical and resource implications.

**How should I prevent and treat hypothermia?**

The detrimental effects of hypothermia on coagulation, platelet function, and metabolism are well recognised. Major injury directly leads to reduced production of body heat. Prevention of hypothermia is easier than reversal, and the importance of mitigating heat loss is well appreciated. Strategies used to prevent hypothermia are summarised in box 1. Although little direct evidence exists for the efficacy of these measures, their application is rational and supported by a recent National Institute for Health and Clinical Excellence guideline on the management of perioperative hypothermia.<sup>w23</sup>

**How should I manage metabolic acidosis?**

Metabolic acidosis associated with haemorrhagic shock is a product of hypoperfusion. Although correction of metabolic acidosis requires restoration of organ perfusion, volume replacement may need to be deferred until haemorrhage has been controlled. This requirement has led to a search for adjunctive pharmacological treatments to offset the pathophysiological consequences of acidaemia on other organ systems, the coagulation system in particular. The traditional treatment for severe lactic acidosis in critical illness is sodium bicarbonate, but little rationale for its use and no evidence of its effectiveness in general, or in the trauma setting, is available.<sup>22</sup> Administration of sodium bicarbonate produces carbon dioxide, which can require large increases in minute volume to clear. In addition, sodium bicarbonate decreases ionised calcium concentrations by about 10%, which has deleterious effects on coagulation and cardiac and vascular contractility.<sup>22</sup> Tris(hydroxymethyl)aminomethane is a biologically inert amino alcohol capable of accepting hydrogen ions.<sup>23</sup> Clinical experience with this product in trauma patients is limited and the precise role of tris(hydroxymethyl)aminomethane in trauma resuscitation is yet to be defined, although the possible applications are attractive in theory.

**What is damage control surgery?**

The concept of damage control surgery arose from the realisation that the massively traumatised patient lacked the physiological reserve to survive the rigours of complex and prolonged definitive or reconstructive surgery. The aim of damage control surgery is to stop haemorrhage and minimise contamination. Haemorrhage is controlled by temporary clamping, packing, shunting, or ligation, and hollow viscus injuries are either closed or resected without anastomosis.<sup>24</sup> On completion of the procedure, the abdomen is temporarily closed using an improvised or commercially available topical negative pressure dressing, which saves time, helps to minimise the risk of intra-abdominal hypertension, and facilitates observation of the volume and nature of drainage from the abdomen.<sup>24</sup> Planned re-operation to restore anatomy and achieve definitive repair is carried out on return to normal physiology. Damage control surgery is associated with potential morbidity and should be employed judiciously.

SUMMARY POINTS

Trauma resuscitation must address all three components of the “lethal triad”: coagulopathy; acidosis; and hypothermia

Damage control resuscitation integrates permissive hypotension, haemostatic resuscitation, and damage control surgery

Coagulopathy is common in patients with haemorrhagic shock

In trauma patients predicted to require massive transfusion, administration of fresh frozen plasma, packed red blood cells, and platelets in a 1:1:1 ratio (of individual units) is associated with improved survival

Recombinant factor VIIa, cryoprecipitate, and tranexamic acid can be considered adjunctive treatments for coagulopathy

Damage control surgery is a surgical strategy aimed at restoring normal physiology rather than anatomical integrity; however, this component of damage control resuscitation should not be applied in isolation

No randomised controlled trial has evaluated the concept of damage control surgery. A small study of patients with severe penetrating abdominal trauma showed a survival benefit for those treated with contemporary damage control techniques compared with historical controls (90% v 58%; P=0.02).<sup>w4</sup> A large non-systematic review published in 1997 reported an overall mortality of 50% and morbidity of 40% with damage control surgery, but the heterogeneity of patients and injuries and the lack of a control group make it difficult to draw meaningful conclusions from this study.<sup>25</sup>

Damage control surgery has nevertheless become an accepted part of the trauma surgeon’s armamentarium,<sup>24</sup> but is now viewed as a component of damage control resuscitation. Damage control surgery should not be practised in isolation. The advances in damage control resuscitation techniques might in the future permit definitive surgical procedures, resulting in a decreased need for damage control surgery. At present, however, no data support this hypothesis.

Conclusion

Damage control resuscitation continues to evolve. Many of the concepts underlying this technique have come from meticulous evaluation of the process and outcome of military practice.<sup>1</sup> Lessons learnt are now redefining the care of the most severely injured patients in civilian practice.

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ADDITIONAL EDUCATIONAL RESOURCES

Trauma.org (<http://www.trauma.org/index.php/>)—Independent trauma education and information website

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