Damage Control Resuscitation of the exsanguinating trauma patient: Pathophysiology and basic principles.

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Abstract

Damage Control Resuscitation (DCR) is a systematic approach to major exsanguinating trauma incorporating strategies of permissive hypotension, haemostatic resuscitation and damage control surgery. In this article we review current literature regarding the pathophysiology of massive haemorrhage: the "lethal triad" of coagulopathy, acidosis and hypothermia, and integrates this with an introduction to the components of DCR.

Introduction

Damage Control Resuscitation (DCR) is a systematic approach to major exsanguinating trauma that modifies current initial resuscitation algorithms and early management protocols.

Incorporating three key concepts of permissive hypotension, haemostatic resuscitation and damage control surgery, it has shifted emphasis to prompt control of haemorrhage and correction of coagulopathy prior to definitive management. It is defined by Hodgetts et al as "a systemic approach to major trauma combining the <C>ABC paradigm (catastrophic bleeding, airway, breathing, circulation) with a series of clinical techniques from point of wounding to definitive treatment in order to minimise blood loss, maximise tissue oxygenation and optimise outcome" [1].

DCR has its origins in the discovery of trauma-induced coagulopathy in the Vietnam War and the use of early rapid transfusion seen in the 1982 Falklands conflict, and has evolved as a true trauma system during the conflicts in Iraq and Afghanistan[1,2].

This evolution in trauma care has developed from a greater understanding of the pathophysiology of exsanguinating haemorrhage. This article provides an introductory review of current knowledge and guidelines in Damage Control Resuscitation, and briefly considers its military and civilian applications.

Pathophysiology of exsanguinating haemorrhage

Massive haemorrhage has been reported to account for up to 50% of all trauma-related deaths[3]. In addition to blood loss alone, haemorrhage produces a cascade of three key physiological interactions encapsulated by the term the "lethal triad". It is this combination of coagulopathy, hypothermia and acidosis that results in a global haemostatic deficit, increasing the risk of exsanguination. Associated anaemia, hyperfibrinolysis and hypocalcaemia increase the lethality of the triad[3-7].

Acute Coagulopathy of Trauma

Acute traumatic blood loss activates the normal coagulation pathway, but massive injury can defeat the normal haemostatic effect of the coagulation cascade. Continued massive exsanguination and ongoing attempts at clotting deplete the body's stores of coagulation factors. Activation of haemostatic mechanisms in turn trigger anticoagulation mechanisms, particularly the Protein C pathway, further reducing the efficacy of the clotting cascade through inhibition of factors V and VII, reduced fibrinogen use and induced fibrinolysis [7]. Coagulopathy of trauma chiefly results from consumption of blood coagulation products, coagulation factor dilution, and abnormal anticoagulation pathway activation, culminating in a pathological fibrinolysis[3-7].

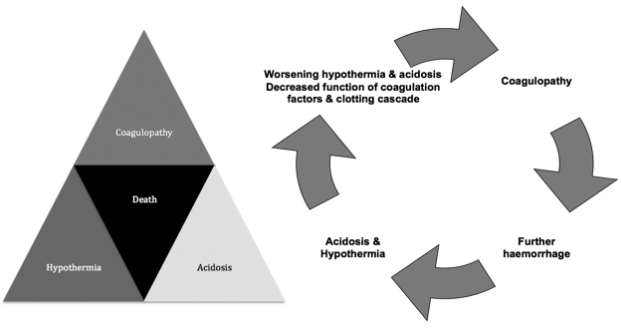

Figure 1 The Lethal Triad

This intrinsic acute traumatic coagulopathy may also be worsened by administration of large volumes of non-blood product intravenous fluids in aggressive resuscitation, diluting coagulation factors, platelets and red blood cells[3-5]. Use of isolated blood components such as red blood cells will further dilute remaining coagulation factors. Choice of intravenous fluid

may also contribute to coagulopathy. Studies show that administration of hydroxyethyl starch 130/0.4 exponentially depletes fibrinogen, prothrombin, and factor X and XIII while 5% hypertonic saline affects platelet function, prothrombin and thrombin times, worsening the coagulation status of the patient[3,9]. A 1994 study of patients with uncontrolled penetrating trauma demonstrated administration of intravenous fluids can increase mortality in the presence of severe uncontrolled haemorrhage[10]. Recently published European guidelines for the management of bleeding following major trauma acknowledge difficulty in identifying an ideal resuscitation fluid or volume with no clear benefit from non-blood products[11].

Acidosis

Acidosis in the exsanguinating patient results primarily from decreased tissue perfusion and a switch from aerobic to anaerobic cellular metabolism, leading to consequent accrual of lactic acid[1,3-7,12]. In addition, acidosis is worsened by an increasing base deficit as a direct consequence of haemorrhage and lactate production, resuscitation with calcium-binding fluids (e.g. Ringer's Lactate) or those containing supra-physiologic concentrations of chloride[13], and the infusion of stored red blood cells that have an increased lactate concentration and elevated base deficit as a consequence of RBC ageing[14,15].

The increased concentration of hydrogen ions acts to disrupt the interaction of coagulation complexes FVIIa, FVIIa/Tissue Factor complex and prothrombinase complex (FXa/FVa) with negatively-charged phospholipid receptors on the surface of activated platelets[5,11]. This inhibition has been found to reduce the activity of FVIIa by 90%, FVIIa/TF complex by 55% and the rate of prothrombinase complex-mediated activation of prothrombin by 70% at a pH of 7.0[3,12,16].

Acidosis further impairs haemostasis through a reduction in the affinity of Ca^{2+}-binding sites on plasma proteases, an increase in fibrinogen degradation by up to 1.8 times normal rates, and a reduction in platelet numbers by up to 50%[4].

Measurement of both serum lactate and base deficit is recommended early in the assessment of haemorrhagic shock to determine the degree of physiological disruption, and should be repeated in order to monitor the response to resuscitation[11].

It has also been postulated that the use of crystalloid fluid, in particular normal saline, in the resuscitation of the exsanguinating patient may worsen acidaemia through the development of a hyperchloraemic acidosis[12].

Hypothermia

Temperature control is a critical factor in the successful management of the trauma patient. Traumatic injury also induces hypothermia by altering the patient's own thermoregulatory mechanisms, reducing shivering, and affecting normal tissue metabolism, so reducing intrinsic heat production[8].

Preventing further external exacerbation of hypothermia is vital. Conductive and radiated losses during the "exposure" phase of trauma management and evaporative losses from wet or soiled clothing need consideration.[8,11,12]. Fluid resuscitation with cool or room temperature fluids and any surgical procedure also contribute to central cooling of the patient by introducing cold fluids to the body's core and/or exposure of peritoneal and pleural surfaces during surgery[10,11].

Acute traumatic coagulopathy is exacerbated by hypothermia, through inhibition of platelet receptor GPIb-IX-V and von Willebrand factor, decreased fibrinogen synthesis and an absolute reduction in physiologic fibrinolytic inhibitors e.g. alpha-2 antiplasmin at lower body temperatures[4,8,12].

These clinically significant effects are present even in moderate hypothermia. At 35°C all coagulation factors decrease their function, with factors XI and XII functioning at only 65% of normal. At 33°C, there is <50% of the usual clotting factor activity observed in normothermic patients, and at 33°C the activity of factors XI and XII is reduced to 17% and 32% respectively[3,12].

Beyond the lethal triad: Hyperfibrinolysis, Hypocalcaemia and Anaemia

Paradoxical hyperfibrinolysis in trauma results from tissue plasminogen activator release due to endothelial damage and restriction of plasminogen activator inhibitor-1 function throughout the vasculature [3,12]. The normally beneficial effect of restricting clot propagation to the site of injury is lost as instead there is a global pathological fibrinolytic response in these severely-injured patients.

Antifibrinolytic agents have been suggested as an option in the bleeding trauma patient[11]. Tranexamic acid and epsilon aminocaproic acid have both been recommended as adjuncts to reduce bleeding in major trauma[11,17]. The recently published CRASH-2 multi-centre randomised controlled trial showed that "tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study"[14].

Circulating ionized calcium (Ca_i^{2+}) concentration is known to be a critical factor in fibrin clot stabilization and the propagation of the coagulation cascade, and there is evidence that concentrations of less than 0.6-0.7mmol/L are associated with an increase in coagulation defects[18].

It has been suggested that Ca_i^{2+} concentrations should be kept above 0.9mmol/L in order to avoid worsening coagulopathy and possible cardiac complications[11].

A decrease in the circulating volume of erythrocytes, and consequent reduction in haematocrit, has been known since the 1980s to reduce platelet efficacy. Turitto and Weiss demonstrated that platelet adhesion increases as haematocrit rises from 10 to 40% under normal linear flow conditions, but shows no further increase between 40 and 70%, and when under abnormal (i.e. traumatic) conditions, there is a linear, proportionate increase in platelet efficacy as haematocrit rises from 10 to 70% [3,20].

Combined with the critical contribution of ADP for platelet activation by red blood cells, it is apparent that haemostatic control requires haematocrit values beyond those required for normal oxygen transport. It is possible that in patients with uncontrolled haemorrhage despite optimum resuscitation (e.g. by avoiding excessive intravenous fluid administration), avoiding a decreasing haematocrit and haemoglobin concentration may improve haemostasis[3]. It is worth noting that the low levels of ADP in banked blood mean that the best option to maintain ADP stores is clearly to minimise the loss of the patient's own blood rather than rely on transfused bank blood to raise the haematocrit, a key goal for managing any exsanguinating patient.

Damage Control Resuscitation: Permissive hypotension, haemostatic resuscitation and damage control surgery

Permissive hypotension

Permissive hypotension, also known as hypotensive resuscitation, is the restriction of fluid administration until exsanguinating haemorrhage is controlled, accepting in the process a limited period of deficient end-organ perfusion. The goal is to maintain a systolic blood pressure of approximately 90mmHg (approximated clinically by a palpable radial pulse), thus ensuring a mean arterial pressure adequate to maintain continued (albeit deficient) end-organ perfusion, while controlling blood loss and allowing optimum coagulation and consolidation of haemostatic mechanisms at sites of injury[5, 21]. Additional resuscitation endpoints include heart rate, urine output and level of consciousness. Bickell's 1994 study demonstrated an in vivo practical benefit from this approach in the hypotensive penetrating trauma patient[10].

Hypotensive resuscitation has a number of limitations; it is said to be only useful in the first hour following traumatic injury and for this reason is now included in the resuscitation guidelines of a number of ambulance services[22]. After this time the target blood pressure reverts to a normal level of 110mmHg[23]. Similarly, patients with head injuries, blast injuries and children less than 12 years old are not suitable candidates for resuscitation using hypotensive principles due to complicating factors related to fluid shifts and variation in physiological functional reserve[23]. Finally, accurately measuring blood pressure in the field can be difficult and rapidly occurring yet significant changes may be missed using an intermittent measurement method. Continuous intra-arterial blood pressure measurement has obvious benefits but both the availability of equipment to do this and the time to insert a cannula clearly limits its acute use.

Permissive hypotension should be used as a specific goal-directed therapy aimed at producing a systolic blood pressure of 90mmHg, reduction of tachycardia to less than 100bpm, a urine output of greater than 0.5mls/kg/hr, and improving conscious level, provided that doing so does not delay the transfer of the patient to theatre[23]. It has been suggested that fluid should be administered in boluses of 250ml, and responses to therapy monitored using a combination of parameters including central venous pressure, mean arterial pressure, central venous pH, lactate, base deficit, haemoglobin concentration and central venous oxygen saturation >70% where this monitoring is available[11,23].

Fluid choice is crucial in this setting, and there remains a marked disparity in recommendations, with 0.9% sodium chloride recommended (on the basis of cost) by the National Institute of Clinical Excellence in the United Kingdom, Hartman's solution advocated by the Royal Centre for Defence Medicine at the University of Birmingham for its theoretically reduced likelihood to contribute to a hyperchloraemic metabolic acidosis in patients already predisposed to acidosis, and low-volume hypertonic saline/dextran advocated by some members of the military community[23-25]. It will inevitably fall to individual institutions to define their own guidelines until further research provides definitive evidence as to the most appropriate fluid for use in hypotensive resuscitation. International consensus recommendations can be very helpful to assist institutional guideline development[11].

Haemostatic Resuscitation

Haemostatic resuscitation is the early use of whole blood or combined replacement blood components as primary resuscitation fluids, and aims to prevent dilutional coagulopathy and treat the intrinsic coagulopathy, described above, through the replacement of each blood component in the same ratio as it is lost through haemorrhage[11,23,26-28].

Fresh whole blood is frequently unavailable for correction of massive bleeding, particularly in the civilian trauma setting due in part to cost and logistic issues but mainly to the need to undertake viral testing of donated blood. Because of this, a significant amount of research into the use of blood-component combinations has been undertaken. Trauma patients generally die as a result of truncal haemorrhage (secondary to blunt or penetrating trauma), head injury or multiple organ failure. Death rates have been used as measures of the success of various haemostatic resuscitation ratios of packed red blood cells: fresh frozen plasma: platelet concentrate. The vast majority of evidence is based on historical non-randomized controlled trials. However there have recently been a number of attempts at providing a better evidence base for the use of recombinant blood products[11,27-30]

Recent studies[28-31] have shown that higher ratios of PRBC:FFP:Platelets in the order of 1:1:1 significantly increase the number of patients surviving massive haemorrhage (37% reduction in mortality in troops resuscitated with PRBC: FP in the ratio 1:1 (12 deaths due to haemorrhage from 31 total deaths) compared to those resuscitated with the traditional 1:8 ratio (19 deaths due to haemorrhage from 20 total deaths)[31].

Other factors that need to be considered in haemostatic resuscitation include plasma fibrinogen levels and calcium concentrations, for reasons described above.

Plasma fibrinogen should be replaced if levels fall below 1.0g/L[29] or 1.5g/L[11], in settings where other conventional treatments have failed, with cryoprecipitate or fibrinogen concentrate[32]. Some current recommendations use formulae to administer fibrinogen concentrates without measurement as part of a massive transfusion protocol[11].

In situations of exsanguinating haemorrhage where conventional treatments have failed, it has been suggested that there is a role for the use of recombinant factor VIIa, at a dose of 100mcg/kg. One hundred and eight incidents of recombinant factor VIIa use in trauma, across 19 hospitals, had been reported to the Australian and New Zealand Haemostasis Registry by 2007. Of the reported cases 87% were related to blunt trauma, 10% to penetrating trauma. Massive haemorrhage was successfully controlled with rFVIIa use in 59% of cases, with subsequent analysis revealing reduced efficacy in situations of severe acidosis and hypothermia. Consequently, predictors of successful use of rFVIIa appear to be pH, temperature and injury severity score. These findings appear to be borne out by US experiences with rFVIIa in the combat setting[33,34].

Research is currently underway into the role of thromboelastography and thromboelastometry in the management of acute coagulopathy of trauma. These methods of assessing coagulation deficiencies are felt to be better suited to trauma management than other plasma-based investigations of coagulation (e.g. Activated partial thromboplastin time, Prothrombin time)[34], and with ongoing research and development into point-of-care testing, will likely lead to significant changes in the assessment of coagulation in trauma. Recently published guidelines recommend thromboelastometric monitoring in massive transfusion protocols and haemostatic resuscitation[11].

Damage Control Surgery

Damage control surgery aims to stop haemorrhage, minimise wound contamination and allow optimisation of physiological function. The traditional surgical goal of definitive management of anatomical defects should be delayed to later definitive operation(s). Rapid assessment and commencement of resuscitation is required in the field or emergency department and priority needs to be given to early transit to the operating theatre. Crucial to the principles discussed in this article is prevention of progression to the lethal triad. Rapid initial surgery is vital and principally involves haemostasis. This staged approach requires close co-ordination between pre-hospital teams, emergency, surgeon, anaesthetic team and intensive care unit and is the final step in the damage control resuscitation paradigm[36-38].

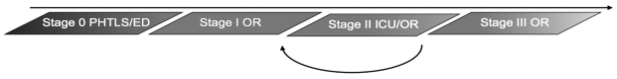

Figure 2 Damage Control Surgery

Applying Damage Control Resuscitation in the military and civilian trauma settings

The use of damage control resuscitation principles has been developed and readily adopted in the military setting and is a key component in US, British and Australian military medical response to combat-related trauma. Given the prevalence of major trauma in the Australian population (2,386 hospitalised major trauma patients in NSW in 2006[40]) there is marked scope for expansion of these principles to the civilian trauma environment.

The vital steps of controlling external haemorrhage, rapid assessment of bleeding site and early surgical control of haemorrhage should to be addressed by procedure and policy on a system-wide basis, incorporating ambulance and other emergency medical services through to definitive treating medical team(s)[23]. For example, strategies to target both patient temperature and higher PRBC:FFP:Platelets

replacement ratios early are immediately applicable with common goals of treatment from the road crew, through the emergency room and further into the hospital admission[12].

There is an argument for frequent updates of the evidence in this approach to exsanguinating trauma, however further research is still required on the use of DCR for management in specific injury-groups, notably blunt trauma, head injury and the paediatric trauma population, and on the role of permissive hypotension in the management of paediatric patients[40]. Hypotension in brain trauma remains contraindicated due to the evidence-base for associated poor outcomes[41].

Conclusion

The Damage Control Resuscitation paradigm incorporates a better understanding of massive exsanguination, provides treatment goals based on this and suggests modification of currently accepted resuscitation algorithms to improve survival for this specific group of trauma patients.

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