

Therapeutic approaches in trauma-induced coagulopathy

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Coagulopathy is a phenomenon which is a life threatening complication in the trauma patient who has sustained significant injuries and blood loss. With our increasing understanding of the mechanisms which drive the coagulopathy and the availability of new treatment options, most notably recombinant factor VIIa (rFVIIa), we are now able to treat those patients who have had a massive traumatic haemorrhage with greater efficacy. This paper reviews the current considerations in dealing with patients with trauma-induced coagulopathy and offers a strategy for their management.

Key words: **Trauma - Consumptive coagulopathy - Critical care - Blood transfusion.**

Our knowledge of effective therapy for the victims of major trauma continues to evolve and the prevention and management of major coagulopathy associated with trauma is of great importance. The primary issues remain difficult to treat effectively in the early resuscitation of an unstable patient; these are the combination of consumption of coagulation factors and platelets and also their ongoing loss due to haemorrhage. The whole approach to the trauma patient has changed over recent years with the acceptance that in major haem-

orrhage, excessive resuscitation may worsen the outcome and that a 'damage control' strategy may improve outcome. These evolutions in trauma care require a multidisciplinary approach from pre-hospital to in hospital resuscitation for optimal outcomes. A combined approach requires pre-hospital teams, emergency physicians, trauma surgeons, anaesthetists, intensivists and radiologists to achieve rapid haemostasis, re-warming of the patient back to normothermia and adequate resuscitation in a goal directed manner.¹

There have been recent innovations, which are likely to be increasingly important in the therapeutic approach to trauma-induced coagulopathy, which will be discussed in this manuscript. We will discuss incidence and aetiology, monitoring of coagulation, strategies to prevent or limit coagulopathy, the role of conventional therapy, and the use of newer novel haemostatic agents, in particular the role of recombinant activated factor VII (rFVIIa).

Incidence and etiology

Haemorrhagic shock is the second most common cause of death in trauma patients

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arriving at hospital, and is the commonest cause of death in the early phase of hospital treatment. However the vast majority of trauma patients do not develop a life threatening coagulopathy.² Overall around 8% of trauma patients receive blood transfusion of packed red cells and only a fraction of these require the transfusion of other blood products.³ This relative infrequency of massive haemorrhage and major coagulopathy emphasises the need to have protocols and procedures in place to cope with the problems when they arise.

The development of coagulopathy associated with trauma involves a combination of many factors including:

- haemodilution
- consumption of coagulation factors and platelets
- acidosis
- hypothermia
- hypocalcaemia
- disseminated intravascular coagulopathy (DIC)
- anticoagulant drugs for comorbid conditions.

The eventual clinical scenario of worsening coagulopathy and ongoing haemorrhage may become increasingly difficult to treat. With the disruption of blood vessels there is bleeding, loss of red cells and both the loss and utilization of coagulation factors and platelets. This leads to a vasoconstriction to maintain blood pressure and mobilization of tissue fluid in an attempt to restore circulating volume. Therefore, already prior to any intervention there has been haemodilution. This problem is compounded by the administration of intravenous fluids, normally in the form of crystalloid. Unfortunately haemodilution will occur with the administration of all intravenous fluids with the exception of fresh whole blood. While fresh whole blood has been recognised as a superior resuscitation fluid in the bleeding patient, and reports of the use of fresh whole blood in recent conflicts in the military setting are set to reconfirm this, the reality is that it is rarely available. The majority of hospitals will use a combination of packed red cells and blood

products, all of which will further haemodilute a bleeding patient.^{3,4} The average unit of packed red cells contains only 35mls of plasma and over one third of the volume is added suspension fluid.

Regardless of which fluid is used it is also increasingly recognised that administration of excessive fluid in the face of ongoing major haemorrhage is unlikely to improve the situation and may in fact worsen outcome by disrupting clot and worsening haemorrhage. For this reason delayed or restrictive fluid resuscitation policies are increasingly adopted until the haemorrhage has been controlled.^{5,6} Ongoing bleeding and hypotension leads to inadequate tissue perfusion and a resulting lactic acidosis. Acidosis is itself an independent factor contributing to the development of coagulopathy due to alteration of pH dependent kinetic enzyme reactions of coagulation factors and platelet aggregation.

Coagulopathy, acidosis and hypothermia are well described as the “lethal triad” for the trauma patient.^{7,8} Hypothermia is a major factor influencing coagulopathy and outcome. The development of hypothermia starts at the time of injury with reduced heat production from decreased motor activity and increased loss through immobilisation and exposure. On arrival at hospital the administration of fluids at less than 37 °C, further exposure for examination and investigation and the use of anaesthetic agents all continue the process of heat loss.⁹ While there is some evidence that hypothermia may attenuate the inflammatory response following haemorrhagic shock,¹⁰ few would advocate the use of hypothermia as a therapeutic option as the weight of evidence shows its importance as a risk factor for mortality.^{11,12} Even small reductions in normal temperatures below 37 °C results in slower coagulation enzyme kinetics; the most sensitive of these is the vWF induced binding of GP Ib/IX/V. In addition, hypothermia will also exacerbate the acidosis and further worsen the coagulopathy. Transfusion of red cells and other products as well as diluting the coagulation factors and platelets can also significantly contribute to both the acidosis and hypothermia. Packed red cells are stored at

1-6 °C and after 2 weeks have a pH less than 7 due to a combination of citrate it being venous blood with a low pH to begin and the generation of acid from glycolysis during storage. Citrate may also cause hypocalcaemia when infused in massive transfusion amounts, when calcium as a cofactor in many steps of coagulation may need to be replaced in this setting.

There are also occasions when the initial dilutional coagulopathy is also followed by the development of DIC. DIC represents a major disruption of the normal coagulation equilibrium characterised by the rapid consumption of coagulation factors and platelets. It is seen particularly in patients who have suffered a traumatic brain injury or long bone fractures associated with fat emboli. The exposure of high concentrations of tissue factor and phospholipid-rich tissue to the intravascular compartment promotes the systemic activation of coagulation.¹³

Often in the acute trauma setting a clear medical history is not available and it can be many hours before a full drug history is available. With our aging but active populations with cardiovascular disease it is increasingly common to find patients who are taking cardio-protective anti-platelet therapy or other forms of anticoagulant medication. Agents such as aspirin or clopidogrel have a profound effect on platelet function and will have a predisposition for continued bleeding despite apparently normal coagulation tests. Formal anti-coagulation, usually with warfarin, will present a more obvious problem and is readily identified from the prothrombin time (PT) or international normalised ratio (INR). Patients suffering from renal impairment will also have impaired platelet adhesion and aggregation. Those with liver disease will have a reduced ability to synthesise coagulation factors as well as clearance of activated factors. In a serious liver injury the above should also be considered.

Monitoring

Monitoring of a developing coagulopathy begins as soon as they arrive in hospital

by regularly taking blood samples for analysis in the laboratory. Haemoglobin concentration, platelet count, PT, activated partial thromboplastin time (APTT) and fibrinogen concentration as well as blood grouping and cross matching should be carried out as early as possible. These tests are cheap, reproducible and the results should be available in around 30 min. While that turn-around time may appear reasonable it is problematic in the massive transfusion situation where the results lag behind the clinical situation and are only therefore of limited utility in determining immediate or empiric therapy. A low platelet count within the first day is very important and an indicator of massive haemorrhage and targeting a level of $100 \times 10^9 \text{ l}^{-1}$ is recommended for actively bleeding patients. Platelet counts tend to fall over the first 72 hours and a low count is common on day 3. PT and APTT are more susceptible to derangement in the initial phase of a trauma. When the values are greater than 1.5 times normal then they are recognised as requiring ongoing correction. Together these tests will pick up abnormalities in coagulation due to a single or multiple deficiencies in coagulation factors, but not identify them. Fibrinogen concentration is the earliest measurable factor to fall and a concentration of less than 1.0 g litre^{-1} is indicative of a severe haemodilutional coagulopathy or developing DIC. The PT, APTT, platelet count and fibrinogen concentration should be measured frequently and in proportion to the ongoing resuscitative needs of individual patients.

Thromboelastography (TEG®) can be a very useful monitoring tool as it gives real time analysis of clot formation.¹⁴ Although well established in the field of liver transplantation and cardio-pulmonary bypass it has yet to gain popularity and be validated in the acute trauma setting, particularly as it is time consuming and requires a skilled operator to perform and interpret the results.

In addition to monitoring of the patients coagulopathy, attention should also be paid to the contributory factors, most principally the body temperature and acidosis. A central temperature probe should be placed as

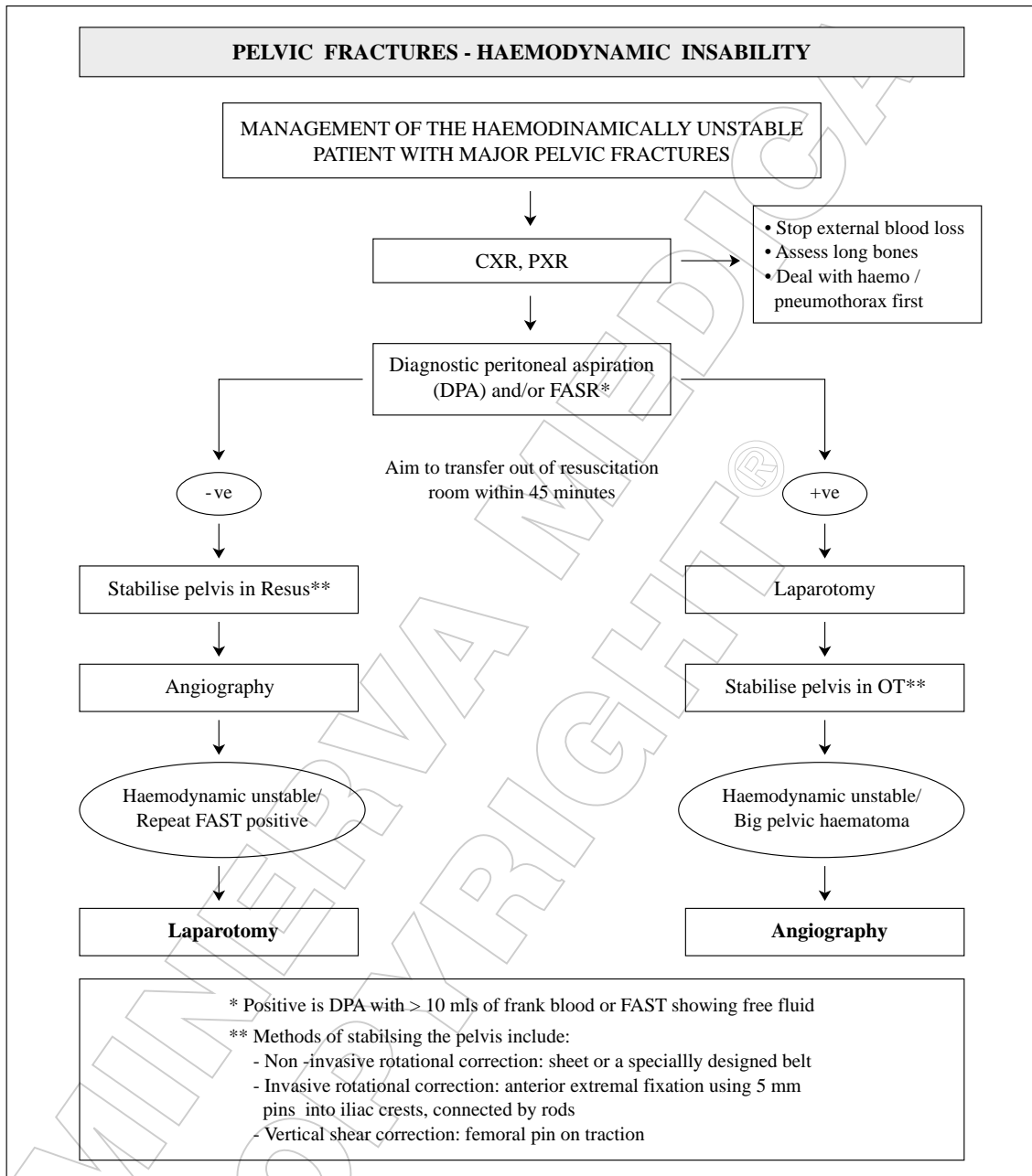


Figure 1.—Damage control surgery approach to massive haemorrhage. Modified from Liverpool Hospital Trauma Handbook.

early as possible in the resuscitation to allow continuous monitoring and active measures to re-warm or maintain body temperature should be started. Regular blood gas analysis is required to manage the acidosis and to

assess the continued adequacy of tissue perfusion and oxygenation. The correction of acidosis and hypothermia are at the core of assessing the adequacy of resuscitation in these patients.

Damage control strategies

The optimal management of these patients requires a comprehensive understanding of the strategies available to reduce the risks of ongoing haemorrhage and metabolic deterioration. An entire issue of the journal *Injury* was dedicated to “damage control” strategies in July 2004. This included a section on the implications of damage control surgery for intensive care, which explored management issues related to coagulopathy and hypothermia in major trauma patients requiring the damage control approach.¹⁵ The principle to be emphasised is recognising when there is no further benefit to the patient from continued operative intervention, and definitive surgical procedures, if still required should be carried out after correction of the serious metabolic abnormalities. Usually all surgically controllable bleeding will have been dealt with at the time of operation and the ongoing haemorrhage is likely to represent bleeding from a site that cannot be managed in the operating room. Some of these patients however, may benefit from interventional radiology prior to or after surgical intervention, with angiography followed by embolisation of identified actively bleeding vessels. This strategy has been credited with improved outcomes¹⁶ and has led to the introduction of local guidelines that aim to reduce ongoing bleeding and metabolic and coagulopathy deterioration (Figure 1).¹⁷ With increasing radiological experience this approach of urgent angiography is being considered for an increasing variety of patients including those with major pelvic injury, complex hepatic injury, splenic injuries, retroperitoneal, pelvic or deep muscle injuries. A contrast blush seen at angiography indicates active arterial bleeding and the need for embolisation. Angiography before damage control laparotomy may also be indicated if there is a very high suspicion of a bleeding lesion that may be amenable to embolisation.

Preventing and treating hypothermia

Temperature control involves heat generation, cerebral temperature control and heat

loss by conduction, convection, evaporation, and radiation. Those at the extremes of age are most susceptible. In the absence of preemptive treatment, heat loss begins at the scene and continues in the emergency department, where the patient is uncovered and exposed to a large patient–room temperature gradient and is compounded by reduced perfusion, immobility, cold fluid and procedures. General anaesthesia, blood loss, and further exposure of body cavities at surgery rapidly result in severe hypothermia.¹⁸ A temperature $<35^{\circ}\text{C}$ is associated with reduced cardiac output, metabolic acidosis, and coagulopathy in its own right. These patients have increased fluid, transfusion, vasopressor and inotropic requirements, and more organ dysfunction, mortality, and prolonged intensive care unit stay.¹¹ A temperature less than $<34^{\circ}\text{C}$ is further associated with inhibition of platelet aggregation and dysfunction of intrinsic and extrinsic coagulation factors and is used as an indicator for DCS.¹⁹ These processes emphasize the need for prevention and effective warming strategies.

Maintaining a thermo-neutral temperature (up to $>28^{\circ}\text{C}$) may be impractical for many situations but emphasizes the degree of heating required to prevent heat loss. Keeping the patient covered and dry and providing ventilation gases that are humidified and warmed should be routine. Forced air warming devices are popular and an efficient method of warming from hypothermia. They result in less core temperature after-drop and a 6-10 times faster when compared with passive and inhalation warming techniques. The majority of patients can be rapidly re-warmed by using these techniques and ensuring all fluids administered are warm.

All fluids administered should be warm and there are numerous devices on the market to provide consistent warming of fluids at both low and high infusion rates. High capacity fluid warmers are capable of warming fluid from 4°C to body temperature at flow rates up to 0.5 L/min to 1.5 L/min. These devices have been credited with improved resuscitation of major trauma, reduced requirements for fluid/blood products, less coagulopathy, more rapid correction of aci-

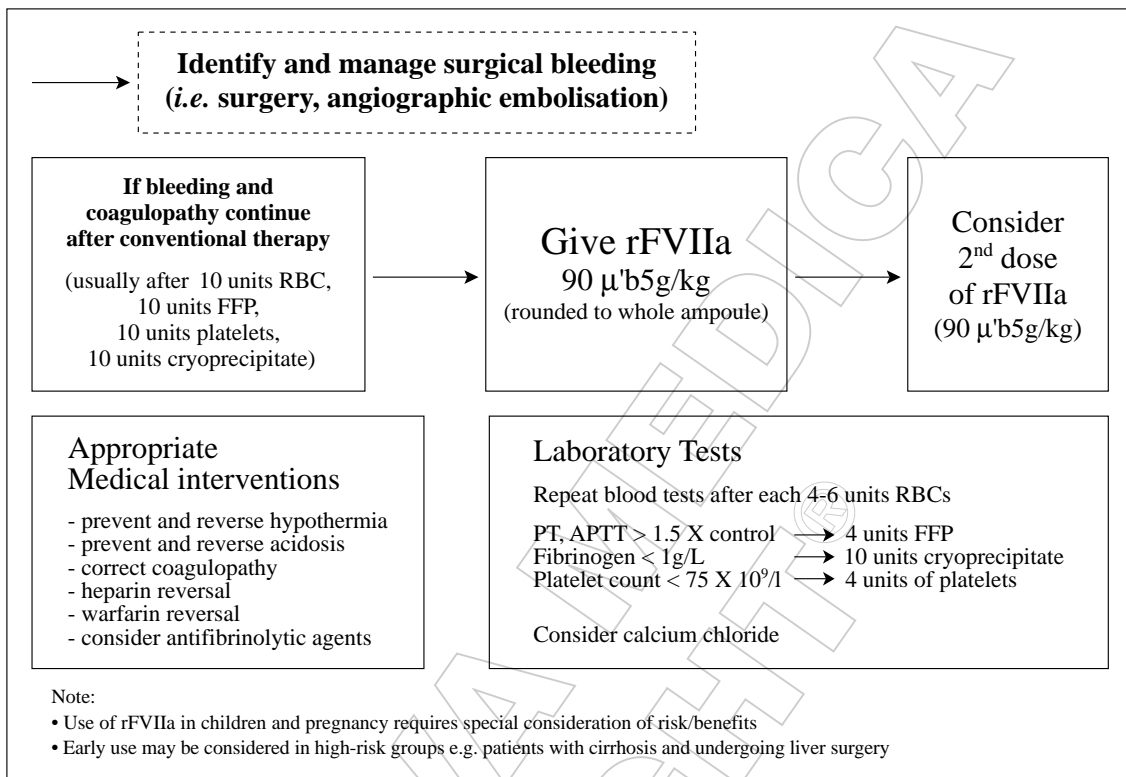


Figure 2. Approach to the trauma patient with major haemorrhage and coagulopathy unresponsive to conventional therapy. Modified from Liverpool Hospital massive transfusion guidelines.

dosis and hypothermia, and fewer hospital complications,²⁰ but increase the risk of excessive fluid administration that may worsen outcome.

The more severe the hypothermia, the more justification for aggressive warming, including extracorporeal techniques. Extracorporeal re-warming is possible using several techniques and is likely to see increased popularity given the increasing availability of simple pumps and heparin-bonded circuits. Depending on the technique used, extracorporeal re-warming can warm at rates of 4-50 °C per hour. It is suggested that if the temperature drops below 33 °C, aggressive extracorporeal re-warming (arteriovenous or venovenous) should be considered. The knowledge that despite replacement of clotting factors and platelets, normal coagulation will not occur until the core temperature exceeds 34 °C adds support to this approach.²¹

Blood product administration

While the aim of volume resuscitation is to restore circulating volume and oxygen delivery, patients who have lost >30% of their circulating volume are likely to need the transfusion of red cells to avoid tissue hypoxia and subsequent acidosis. In the life threatening situation Group O-Rh (D) negative (O-Rh-positive is acceptable for males and females beyond child bearing age) blood should be given until the patients' blood grouped and cross-matched. The decision to give blood in the acute trauma setting is a clinical one made usually before the results of the first blood count and clotting studies are available. The clinician overseeing trauma management will give blood based on the patient's risk factors for complications of inadequate oxygenation, such as the rate of blood loss, cardiorespiratory reserve, oxygen requirement and atherosclerotic disease.

The pulse rate and blood pressure, other invasive measured variables and assessment of arterial blood gases will assist in the decision making process.

When treating massive haemorrhage it is important to recognize that coagulopathy is often inevitable, while doing everything possible to prevent and minimize it. A coordinated approach to massive haemorrhage should include the availability of a "Trauma Blood Pack", which should be available on making a single phone call to the blood bank. This could comprise of 10 units of ORh (D) negative (or positive as above) blood, 6 units of platelets (which are now usually supplied as pooled units) and 4 units of (previously thawed) FFP. The platelet count should not be allowed to fall below 50×10^9 and a higher target of 100×10^9 is recommended in the trauma setting, particularly if there is brain injury. When two blood volumes have been replaced, a platelet count of 50×10^9 should be anticipated. A prolonged PT or APTT of greater than 1.5 times normal should be corrected with the repeated administration of FFP. An adult dose of FFP is 12-15mL kg⁻¹ which is typically 4 units of FFP. Fibrinogen concentration should be monitored and when this falls below 1.0 g litre⁻¹, 10 units of cryoprecipitate should be given; this level of fibrinogen may be encountered after 1.5 times the circulating volume has been replaced.

All appropriate attempts to control haemorrhage should be continued during this process.

Role of other agents

Calcium

Citrate in transfused blood decreases calcium concentration and adds to the coagulopathy,²² and rapid plasma protein administration may also decrease ionised calcium levels through the binding of calcium ions to anionic sites. Usually this is a transient phenomenon, dependent on the total dose of citrate administered, the rate of infusion and is unlikely to be significant unless a massive transfusion is being given. Calcium is often

given in an empiric fashion during massive and continuing high volume transfusion but rational calcium replacement may be based on direct ionised calcium measurement. Haemaccel, a gelatin colloid solution has a calcium concentration of 6.25 mMol⁻¹, and its use during trauma resuscitation reduces the likelihood of hypocalcaemia.

Antifibrinolytic agents

There is anecdotal evidence that aprotinin; the protease inhibitor may have a role as adjunctive therapy in the presence of ongoing coagulopathy and potential DIC by decreasing fibrinolysis.²³ The other antifibrinolytic agents, epsilon aminocaproic acid and tranexamic acid may also have roles if excessive fibrinolysis is demonstrated. Adhesive fibrin sealants have demonstrated in animal models an efficient method of achieving haemostasis.²⁴

Reversal agents

Vitamin K should be given to patients who are on warfarin therapy and protamine should be given to those who have received heparin, although this is unlikely in the trauma setting. DDAVP should be considered for those patients suffering from von Willebrand's disease or chronic renal failure.^{25, 26}

rFVIIa

Recombinant activated factor VIIa (rFVIIa) is licensed for use in haemophiliacs with inhibitors to exogenous factor VIII or IX. There are increasing reports of benefit in non-haemophiliac patients with massive haemorrhage and coagulopathy unresponsive to conventional therapy.²⁷⁻²⁹ Since the first description of its use in a trauma patient rFVIIa has been used to control bleeding in a variety of non-haemophiliac patients who have failed with conventional therapies.

Our cumulative experience includes patients who have suffered multiple injuries from road trauma or assault, post-operative cardiac surgical patients and a patient who had major complications of. Our recent case series showed an improvement in clinical

evidence of coagulopathy, laboratory tests of coagulation and decrease in transfusion requirement in the 48 hours following administration of rFVIIa. This was associated with a good outcome in the majority of cases. The patients were refractory to conventional therapy and were thought to be at imminent risk of dying. rFVIIa may be less effective when given to profoundly hypothermic and acidotic patients and this may need to be considered when using this valuable resource in this setting. Recent evidence suggests that rFVIIa should be effective in enhancing haemostasis in hypothermic patients but its efficacy may be reduced in acidotic patients. It has been suggested that correction of severe acidosis should precede administration of rFVIIa.³⁰

rFVIIa has a good safety profile in the bleeding haemophiliacs. In haemophiliacs serious adverse events occur in less than 1%; however, there remain concerns regarding the agent's potential to induce thrombosis.³¹ Given the nature of the mechanism of action of rFVIIa there are concerns of a potential increased risk of thrombo-embolism, particularly as the patient groups likely to receive it are already at high risk.

The recent published study on rFVIIa in acute intracerebral haemorrhage demonstrated a 7% thromboembolic event rate *versus* 2% in the placebo group, the mortality at 28 days was 29% for patients receiving placebo *versus* 18% for those receiving rFVIIa.³²

The true role of rFVIIa in the management of haemorrhage in trauma patients has yet to be fully established.³³⁻³⁵ Given the availability of rFVIIa and the perceived benefits, institutions are developing local protocols and guidelines for its use. In our institution this has involved multi-disciplinary discussion and production of a guideline document to assist clinicians. Our current guidelines state that if conventional therapy has failed to control the blood loss (usually at least 10 units of RBCs, 10 units of FFP, 10 units of platelets, and 10 units of cryoprecipitate will have been given), and bleeding with coagulopathy continues, and all surgical and embolisation procedures have been attempted, and consultation with a haematologist

confirms optimal conventional therapy and the appropriate dosage of rFVIIa, then a dose of 90 mcg/kg rFVIIa may be given. The dose is rounded up or down to the nearest 1.2 mg vial size to avoid any wastage. Clinical response is usually obvious within 20 min. If no response within 20 min, a second dose of 90 mcg/kg rFVIIa may be considered. Randomised controlled trials in Australia and other countries are focusing on numerous areas including the use of rFVIIa in paediatric cardiothoracic surgery, intracerebral haemorrhage, liver transplantation, liver surgery and bone marrow transplantation.³⁶

Conclusions

The management of the bleeding trauma patient is complex. The standards of therapy remain the correction of the 'lethal triad' but with growing experience interventional radiology, damage control strategies and the use of novel agents such as rFVIIa appear to be improving the management of coagulopathy and outcome from major trauma.

Riassunto

Approcci terapeutici alla coagulopatia indotta da trauma

La coagulopatia è un fenomeno che rappresenta una complicanza pericolosa per la vita dei pazienti traumatizzati che hanno subito gravi danni ed emorragia. Con la nostra comprensione sempre migliore dei meccanismi che guidano la coagulopatia e con la disponibilità di nuove opzioni terapeutiche, principalmente il fattore VIIa ricombinante (rFVIIa), siamo ora in grado di trattare con maggiore efficacia quei pazienti che hanno avuto una grave emorragia da trauma. Questo lavoro rivede le attuali convinzioni riguardanti i pazienti con coagulopatia indotta da trauma ed offre una strategia per la loro gestione.

Parole chiave: Trauma - Coagulopatia da consumo - Paziente critico - Trasfusioni di sangue.

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