Management of Massive Blood Loss

Asuccessful outcome requires prompt action and good communication between clinical specialties, diagnostic laboratories, hospital transfusion laboratory staff and the Blood Service.

Therapeutic goals

These are;

- Maintenance of tissue perfusion and oxygenation by restoration of blood volume and haemoglobin >8 g/dl
- Maintain platelet count >75 × 10^9/L
- Maintain PT & APTT< 1.5×mean control
- Maintain Fibrinogen > 1.0 g/l
- Arrest of bleeding by:- treating any traumatic, surgical or obstetric source,judicious use of blood component therapy to correct coagulopathy[**32]**.

Initial Fluid Management

Parenteral solutions for the IV resuscitation of hypovolemic shock are classified as crystalloid or colloid, depending on molecular weight. Controversy exists regarding the appropriate choice of resuscitation fluid for the trauma victim with mild to moderate hemorrhage. The focus of this controversy centers primarily on the effect each fluid type has on the lungs. The goal of fluid administration in the trauma patient is to replace volume in order to support cardiovascular function by increasing cardiac preload and to maintain adequate peripheral oxygen delivery [**33]**.

Rapid fluid resuscitation is considered the corner stone of therapy by some authers for the initial management of hypovolemic shock [**15**].

However, there has been controversy over the years regarding the aggressive administration of IV fluids to hypotensive patients with penetrating torso wounds. Research studies from the early 1990 suggest that IV fluids should be delayed until the time of definitive operative intervention **[34]**.

In young patients, volume infusion is typically infused at the maximum rate allowed by the equipment and the size of the cannulated vein until a response is appreciated. In older patients or those with comorbid conditions such as cardiac disease, fluid resuscitation is titrated to response to avoid complications associated with hypervolemia. Attempting to reach normotension by the transfusion of resuscitation fluids is not necessarily the goal. Much time can be lost chasing vital signs with fluid resuscitation when, in some injuries, early definitive operative intervention to stop blood loss is required [**14**].

Crystalloids

Crystalloid solutions are generally safe and effective for resuscitation of patients in hypovolemic shock. Isotonic human plasma solutions, with sodium as the principal osmotic active particle, are used for resuscitation. They can be administered rapidly through peripheral veins due to their low viscosity. Isotonic fluids have the same osmolality as body fluids; therefore, there are no osmotic forces directing fluids into, or out of, intracellular compartments. During resuscitation, isotonic crystalloids are administered approximately 3 to 4 times the assessed vascular deficit to account for the distribution between the intravascular and extravascular spaces. Crystalloids partition themselves in a manner similar to the body's extracellular water content; 75% extravascular and

25% intravascular The majority of complications associated with the use of crystalloid solutions are either because of under treatment or because of overtreatment [**33**].

The use of one specific crystalloid over another is largely a matter of institutional or provider preference. Normal saline is the only crystalloid that can be mixed with blood and blood products. Patients resuscitated with large amounts of normal saline are at risk for developing hyperchloremic metabolic acidosis because its chloride concentration is higher than that of plasma. Lactated Ringer's solution has the advantage of a more physiologic electrolyte composition. Hypertonic saline solutions are crystalloids that contain sodium in amounts higher than physiologic concentrations. They expand the extracellular space, by creating an osmotic effect that displaces water from the intracellular compartments. Hypertonic saline decreases wound and peripheral edema. There is some research to suggest, however, that hypertonic saline resuscitation may contribute to increased bleeding **[14]**.

Most sources agree that the best way to manage hypovolemic shock in trauma patients is the judicious use of warmed IV fluids and blood products. Many trauma centers initially infuse 2 to 3 L of lactated ringers or normal saline and then consider blood products if the patient remains symptomatic. While crystalloids are infusing, the blood bank has time to type and cross-match the patient for transfusion of type-specific blood **[35]**.

Colloids

Colloids are solutions that have a higher molecular- weight species and create an osmotic effect. Colloids remain in the intravascular space

for longer periods than do crystalloids. Smaller quantities are required to restore circulating blood volume. Colloids attract fluid from the extravascular to the intravascular space because of their oncotic pressure. Examples are albumin, hetastarch, dextrans, modified fluid gelatin, and urea bridge gelatin. They are expensive to use and complications have been reported in their use. Albumin has been implicated in decreased pulmonary function, depressed myocardial function, decreased serum calcium concentration, and coagulation abnormalities **[14]**

Hetastarch may cause decreased platelet count and prolongation of the partial thromboplastin time. Several complications have been associated with the use of dextran, to include renal failure, anaphylaxis, and bleeding. Gelatins are associated with anaphylactoid reactions. They also may cause depression of serum fibronectin. Because of the high cost and complication rates, there appears to be no clear advantage to using colloid Solutions [**36**].

Cystalloids Versus Colloids

Proponents of colloid therapy argue that maintenance of the plasma colloid oncotic pressure (PCOP) is necessary to minimize interstitial edema, particularly In the lungs. The concern is that massive crystalloid resuscitation creates an oncotic pressure gradient encouraging movement of fluid from the intravascular space into the pulmonary interstitium. Colloid supporters further propose that since colloids remain primarily in the intravascular space, they are more effective volume expanders, and also are less likely to cause peripheral edema than crystalloids. However, little support is found in the literature to support superior efficacy of one solution over the other [**15**].

Blood products and component therapy

Neither crystalloid or colloid solutions increase oxygen-carrying capacity. Administration of large amounts of fluids can also prove detrimental by diluting hemoglobin levels and contributing to fluid volume overload **[33].**

Blood products are currently the most readily available fluids to increase oxygen-carrying capacity and cardiac preload. However, transfusions carry the risk of various blood-borne pathogens and transfusion reactions. There is considerable debate regarding indications for transfusion. Patients with hemorrhage of up to approximately 20% of their total blood volume can be safely volume replaced with crystalloids in a ratio of 3 milliliter of crystalloid per milliliter of estimated blood loss. During the infusion of crystalloids, the blood bank has time to perform a type and cross match, so that, if needed, type-specific blood is available for transfusion. Most agree that patients with 20% to 40% loss of circulating blood volume, or those demonstrating evidence of hemodynamic instability, and those with blood gas evidence of shock, despite aggressive fluid resuscitation, may benefit from blood transfusions **[15]**.

Blood Types And Rh Issues

The decision to transfuse should be based on the assessment of ongoing blood loss, the patient's ability to compensate, and the availability of cross-matched blood products. Additional considerations are given to the patient's age and presence of comorbidities. Ultimately, type-specific blood products are preferred, but when a patient arrives in apparent shock or extremis, the universal donor type O, Rh negative, is

transfused using a rapid infusor/warmer device. Rh-negative blood may be in short supply; therefore, some hospitals have policies in place that allow Rh-positive Group O, packed red blood cells (PRBCs) to be transfused in men, and women older than childbearing age. The rationale behind this practice is that naturally occurring anti-Rh bodies do not exist, therefore there is no advantage to the use of Rh-negative blood. However, there is some concern that Rh-negative patients may have been sensitized from pregnancy or previous transfusions and could develop a delayed hemolytic transfusion reaction from Rh-positive blood use. This is a rare occurrence; therefore, O-Rh-positive PRBCs are considered the first choice for emergency transfusions, with consideration for the use of O-Rh-negative PRBCs for females with childbearing potential [15].

Some sources recommend that the number of transfusions of (type O) be limited to 4 units, after which type-specific blood should be available in most institutions receiving trauma patients. However, when necessary, type O blood may be continued until the patient stabilizes or type specific is available [**14**].

Type-specific blood is ABO and Rh compatible and is available within less than 15 minutes in most institutions. Type-specific blood has been shown to be safe and effective during emergency resuscitations **[37].**

Massive Transfusion

Trauma practitioners are frequently faced with situations that require decision making to weigh the risks and benefits of massive transfusions. When the decision is made to proceed, there are technological considerations that affect infusion rates. Large bore catheters, as well as high-volume IV tubing, allow for the fastest blood

administration. Pressure bags and/or mechanical rapid transfusion devices further increase flow rates. Remember that normal saline is the only fluid additive that can be used in conjunction with blood product transfusion, Lactated Ringer's solution will cause precipitation of blood within the tubing [**37**].

Blood component support takes time to organise and the supplying blood centre may be several hours away from the hospital. Special transfusion requirements for specific indications, e.g. components suitable for neonates, irradiated components for patients at risk of transfusion-associated graft-versus-host disease, should be taken into account if time permits, but it may be necessary to make a pragmatic decision regarding the relative risks of delaying transfusion or giving components that are not of the appropriate specification [**32]**.

At this writing, component therapy remains the current standard for blood transfusion. It refers to the utilization of the components of whole blood to include RBCs, fresh frozen plasma (FFP), platelets, and cryoprecipitate. One unit of whole blood contains 200 mL of red blood cells and 250 mL of plasma, which contains coagulation factors. Component therapy has several advantages over whole blood, and evidence suggests that the PRBCs and component therapy are as effective as whole blood transfusion without the disadvantages. PRBCs and components are more readily available and are less expensive and easier to store than whole blood. Volume expansion can be accomplished with a combination of crystalloids and PRBCs, Another advantage of component therapy over whole blood is that infusions can be tailored specifically to the needs of the individual patient. Furthermore, PRBCs increase oxygen carrying capacity more efficiently than whole blood. The

disadvantage of whole blood is that platelets are not well preserved, and clotting factors decrease rapidly at blood storage temperatures. For these reasons, PRBC infusion with component therapies are considered the methods of choice for increasing red blood cell mass and oxygen-carrying capacity in hemorrhagic shock [**15**].

Red Blood Cells (RBC)

RBC's carry oxygen to the tissues and should not be used as a primary volume expander. Red cells are likely to be required when 30-40% of blood volume has been lost. Be aware that in the young, the fit and the obstetric patient blood loss can be under estimated . Blood replacement should be clinically guided and based on the patient's response, ensure pre-warming of all resuscitation solutions . Pre transfusion compatibility should be performed where possible. If a pre transfusion cross match is unable to be completed prior to the patient needing blood product transfusion, then un-cross matched Group O Rhesus (Rh) D negative red cells should be used in all females of childbearing age (<50 years). If Group O Rh D negative red cells are in short supply Group O Rh D positive should be used in males **[38]**.

Fresh Frozen Plasma (FFP)

Impaired haemostasis is most probably multifactorial in origin and results from the adverse haemostatic effect of multiple concurrent coagulation factor deficits combined with anaemia, thrombocytopenia, acidosis and hypothermia. The level of fibrinogen falls first; the critical level of 1.0 g/l is likely to be reached after 150% blood volume replacement, followed by the fall of other labile coagulation factors with continued blood loss. Prolongation of the activated partial thromboplastin

time (aPTT) and prothrombin time (PT) to 1.5 times the mean normal value is correlated with an increased risk of clinical coagulopathy. Infusion of FFP should be guided by the volume of blood lost, fluid replaced and by PT, aPTT (>1.5 times mean normal value) and fibrinogen levels. Transfusion of plasma components should be large enough to maintain coagulation factors above the critical level (30%), when there may be inadequate time to obtain results of PT and aPTT. [**39**]

Cryoprecipitate

Cryoprecipitate is most useful in massive haemorrhage as a rapid source of fibrinogen when the fibrinogen is <1.0 g/L. It can be used:

- early in massive haemorrhage as first-line therapy as a source of fibrinogen
- management of dilutional hypofibrinogenemia
- following FFP (if there is persistent hypofibrinogenemia)
- when the fibrinogen level is disproportionately low compared with other factors (e.g. as occurs with fibrinogenolysis).

The dose of cryoprecipitate is generally 2 mL/kg body weight and one unit should increase the fibrinogen level by 0.1 g/L. (roughly 10 bags/70kg individual) [**39]**.

Platelets

Thrombocytopenia can occur reasonably quickly and usually results from haemodilution but maybe due to increased consumption. The rate of decline in patient platelet counts is individual; however the number of platelets each patient has does not correlate with the ability to coagulate. Platelet count should be maintained above the critical level of 50 x 10^{9}/L in a bleeding patient. This level may be anticipated when 2

blood volumes have been replaced. The amount should be based on a combination of clinical criteria and laboratory values.

A higher target level of 100 x 10^{9}/L is recommended for patients with head injury and high velocity trauma. Empirical platelet transfusion may be required when platelet function is abnormal (secondary to antiplatelet therapy**) [40].**

systemic haemostatic agents

Vasopressin analogues

Desmopressin

Desmopressin acetate, 1-desamino-8-D-arginine vasopressin (DDAVP), is a synthetic vasopressin analogue. It is pharmacologically altered from naturally occurring vasopressin by deamination of hemicysteine at position 1 andsubstitution of D-arginine for L-arginine at position 8. These changes virtually eliminate vasopressor (V1 receptor agonist) activity, and enhance the antidiuretic (V2 receptor agonist) action. It also prolongs the duration of action from 2–6 hour to 6–24 hour by increasing resistance to enzymatic cleavage. Desmopressin is also more potent than arginine vasopressin in stimulating the endothelial release of factor VIII and von Willebrand factor into the plasma (V2 receptor mediated effect), where they form a complex with platelets and enhance their ability to aggregate. **.[41]**

This effect, which mimics replacement therapy with blood products, forms the rationale for the use of desmopressin in the treatment of patients with mild haemophiliaAand type I von Willebrand's disease, who have spontaneous bleeding or are scheduled to undergo surgery**.[42]**

For haemophilia A, von Willebrand's disease, uraemic thrombocytopathy, and when used perioperatively, desmopressin is given in a dose of 0.3 mg/ kg and infused slowly because of the risk of acute hypotension. **.[41].**

Plasma concentrations of factor VIII and von Willebrand factor are approximately doubled or quadrupled, reaching a peak 30–60 minute after i.v. infusion.These doses can be repeated as clinically necessary at intervals of 12 to 24 hour, but tachyphylaxis may occur after three or four doses. After i.v. injection, desmopressin has a distribution half-life of 7–8 minute and an elimination half-life of 2.5–4.4 hour**.[43]**

Desmopressin shortens the bleeding time in a variety of congenital platelet function defects. The ability to shorten the bleeding time in these patients is unpredictable and must be assessed individually in each patient. Desmopressin can shorten the prolonged bleeding time in patients with hepatic cirrhosis and in chronic uraemia, despite the fact that von Willebrand factor and factor VIII are within normal levels. It is therefore used to prevent haemorrhage after biopsies or minor surgical procedures or to control acute bleeding in such patients. Patients with prolonged bleeding time secondary to antiplatelet drugs (aspirin or ticlopidine) may also benefit from the effect of desmopressin as it promptly normalizes primary haemostasis and shortens the bleeding time in most of these patients.[**44**]

Antifibrinolytics

Antifibrinolytic agents in current use include the naturally occurring serine protease inhibitor aprotinin, the synthetic protease inhibitor nafamostat and the synthetic lysine analogues aminocaproic acid

and tranexamic acid. Antifibrinolytic drugs should ideally be used only in those situations in which hyperfibrinolysis can be detected. Typical surgical procedures which may be associated with hyperfibrinolysis are operations requiring cardiopulmonary bypass, orthotopic liver transplantation, and some urological and orthopaedic operations. However, antifibrinolytics have also been widely and successfully used in surgical procedures not associated with hyperfibrinolysis. Plasmin, the final enzyme in the fibrinolytic pathway, is a serine protease. It is not surprising, therefore, that inhibitors of serine proteases possess antifibrinolytic properties. They do so by forming reversible enzyme–inhibitor complexes with plasmin and other serine proteases.It is important to note that coagulation enzymes are serine proteases and therefore serine protease inhibitors will possess anticoagulation in addition to antifibrinolytic properties. Lysine analogues reversibly bind to the lysine-binding site on plasminogen, thereby inhibiting the conversion of plasminogen into plasmin on the surface of fibrin (Fig. 6**).[**45**]**

They also prevent plasmin degradation of platelet glycoprotein lb receptors. Lysine analogues can potentially enhance haemostasis when bleeding is associated with primary fibrinolysis (hyperplasminaemia). They should not, however, be used in disseminated intravascular coagulation (DIC) as this may increase intravascular thrombosis, unless low dose heparin is given concomitantly. The reason is that lysine analogues inhibit both circulating plasmin and fibrin-bound plasmin and therefore interfere with the dissolution of clots in small blood vessels, further aggravating the condition. This is at variance with aprotinin, which inhibits circulating plasmin and spares fibrin-bound plasmin. Additionally, clinical studies indicate that antifibrinolytic amino acids are

haemostatically effective even when bleeding is not associated with overt laboratory signs of hyperfibrinolysis.[**46**]

Both drugs have been widely used to prevent or treat bleeding during tooth extraction in haemophilia and some other coagulation disorders. They are used in the management of recurrent epistaxis, upper gastrointestinal bleeding and primary menorrhagia. Moreover, tranexamic acid appears to reduce the frequency of attacks of hereditary and non-hereditary angioneurotic oedema. Epsilon-aminocaproic acid and tranexamic acid have been used in the past to reduce the incidence of re-bleeding in subarachnoid haemorrhage; however, this is not currently adopted because both drugs may induce vasospasm and ischaemic stroke.[**47**]

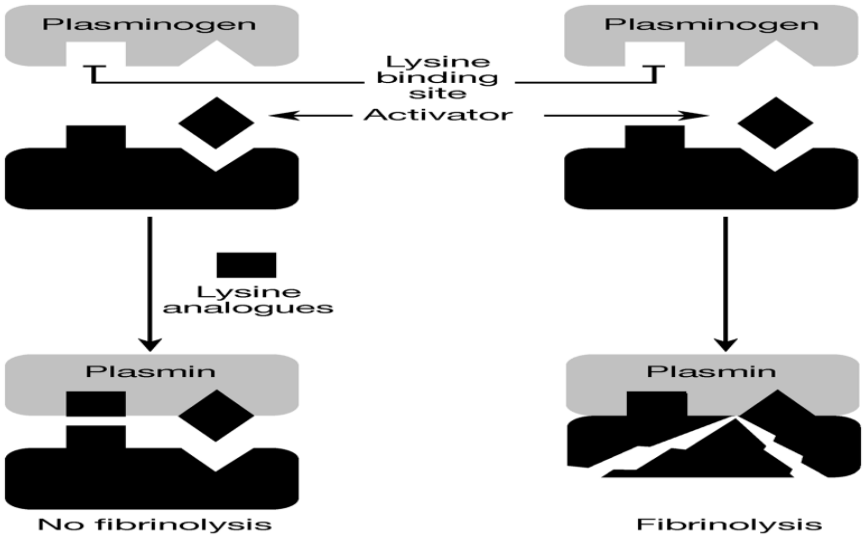

Fig.(6): Mechanism of action of lysine analogues. On the left, EACA or tranexamic of fibrin, even though plasminis acid (lysine analogues) blocks the lysine-binding site on plasminogen,activation of plasminogen on the surface of fibrin. Binding of lysine analogues to plasminogen prevents the breakdown generated (lower left). .[**47**]

Epsilon-aminocaproic acid

Epsilon-aminocaproic acid (6-aminohexanoic acid; EACA) is a competitive inhibitor of plasminogen activation and inhibits plasmin to a lesser extent (at higher doses). It has been used in various doses and regimens in patients undergoing surgery. In general, the recommended dose is 150 mg/ kg as an i.v. bolus before surgery, followed by an infusion of 15 mg/ kg/ hour during the operation. EACA is largely eliminated unchanged by renal excretion and about 35% undergoes hepatic metabolism to the metabolite adipic acid, which also appears in the urine. The renal clearance (116 ml/ min) approximates endogenous creatinine clearance, and total body clearance is 169 ml/ min. The terminal elimination half-life for aminocaproic acid is 1 to 2 hours .[**42]**

Tranexamic acid

Tranexamic acid (trans-4-aminomethyl-cyclohexane carboxylic acid) is a competitive inhibitor of plasminogen activation and, at much higher concentrations, a non-competitive inhibitor of plasmin. Its actions are similar to those of aminocaproic acid, but tranexamic acid is about 10 times more potent in vitro, with higher and more sustained antifibrinolytic activity.Tranexamic acid is usually given as a bolus dose of 10–15mg/kg I.V. before surgery. In cardiac surgery, this is followed by 1mg/ kg/ h for 5–8 hours. However, a wide range of dosage regimens has been used in different surgical procedures. .[**42]** only a small fraction of administered tranexamic acid is metabolized; most is excreted unchanged by the kidney. The dose must be substantially decreased in renal impairment. Pharmacokinetic studies have revealed that tranexamic acid has a volume of distribution of 9–12 litres and an elimination half-life of about 2 hour. There are a number of clinical studies that attest to its effectiveness in decreasing blood loss and transfusion requirement after

cardiopulmonary bypass. There is also some evidence that it may be effective in other surgical procedures.**[48]**

Nafamostat

In 1981, Fujii and Hitomi first reported the use of Nafamostat Mesilate as a synthetic protease inhibitor. It inhibits thrombin, factors Xa and XIIa, kallikrein, plasmin and complement factors (C1r, C1s). As such, it works as an antifibrinolytic, anticoagulant and anti-inflammatory agent. Moreover, it has also been shown to preserve platelet function during cardiopulmonary bypass. Clinically, it has been used in the treatment of disseminated intravascular coagulation and acute pancreatitis. It has also been investigated as an anticoagulant in extracorporeal circuits and as a haemostatic agent in cardiac surgery. Several studies conducted in Japan reported a significant reduction in postoperative blood loss when nafamostat was used in cardiac surgery.[**49]**

Aprotinin

Aprotinin is a naturally occurring 58-residue polypeptide derived from bovine lung with a molecular weight of **6512** Da. It is a powerful inhibitor of plasmin, trypsin, chymotrypsin, kallikrein, thrombin and activated protein C, through the formation of reversible enzyme–inhibitor complexes. **[50]**

The enzymatic activity of Aprotinin is generally expressed in kallikrein inactivator units (KIU), with 1 KIU defined as the amount of Aprotinin that decreases the activity of two biological kallikrein units by 50%.[**48]**

The mechanisms by which Aprotinin exert its haemostatic effects are not fully understood. Studies of perioperative haemostasis have shown that plasma markers of fibrinolytic activity, such as D-dimers, are suppressed during the use of aprotinin. This led to the conclusion that Aprotinin reduces perioperative bleeding by acting as a powerful antifibrinolytic. It inhibits circulating plasmin without interfering with fibrin-bound plasmin, and therefore it does not prevent the dissolution of clots in small blood vessels, an effect that is not observed with antifibrinolytic lysine analogues.[**44]**

At higher doses, Aprotinin also Inhibits kallikrein and thus the intrinsic pathway of coagulation With a subsequent reduction in contact-factor-dependent Fibrinolysis and Bradykinin production. Plasma concentrations Of 125 KIU/ ml are usually needed to inhibit plasmin, whereas concentrations of 300–500 KIU /ml are needed to inhibit kallikrein. There is controversy in the literature regarding the effects of Aprotinin on platelets. Initial studies in patients undergoing cardiac surgery suggested that Aprotinin protects platelets against the initial effect of cardiopulmonary bypass. [**47**]

This has been challenged recently by other studies suggesting that Aprotinin does not influence platelet function. The Currently held view is that the haemostatic effect of Aprotinin is exerted mainly through inhibition of plasmin. Although Aprotinin does not directly affect platelet adhesion or aggregation, it may indirectly protect platelets through the inhibition of various platelet agonists produced during cardiopulmonary bypass, including plasmin.In addition to its haemostatic properties, Aprotinin has multiple actions that may suppress the inflammatory response, particularly at higher dosages. By inhibiting kallikrein,

Aprotinin blocks the conversion of kininogen to the inflammatory mediator bradykinin. It also inhibits the activation of C1 of the complement system; attenuates the release of TNF-a, interleukin (IL)-6 and IL-8 inhibits endogenous cytokine induced nitric oxide synthase induction,decreases bypass induced leucocyte activation and inhibits monocyte and granulocyte adhesion molecule up-regulation. Aprotinin has been used in different dose administration regimens, the most common being a loading dose of 2 million KIU followed by continuous infusion of 500 000 KIU/ hour. .[**51]**

Recombinant activated factor VII

Recombinant factor VIIa (rFVIIa) was originally developed for the treatment of bleeding complications in hemophilia patients with inhibitors against factors VIII or IX. In this group of patients, surgery has always been a challenge as it may result in life-threatening bleeding that is difficult to manage by usual measures. Studies have shown that surgery in patients with high-titter inhibitors against factor VIII or IX can be performed safely using rFVIIa. .[**47**]

Therapeutic effects of rFVIIa begin at doses up to 10 times higher than physiological concentrations of endogenous factor VII. It is therefore used as a pharmacological intervention rather than a mere replacement of a deficient coagulation factor. Recombinant factor VIIa acts by enhancing the natural coagulation pathway through the formation of tissue factor–factor VIIa complex at the site of endothelial damage. This strictly localized effect is what makes rFVIIa different from other haemostatic agents and almost eliminates all undesirable side-effects. Moreover, studies have shown that rFVIIa, when given in supraphysiological dosage, can bind to the phospholipid membranes of activated platelets

where it activates factor X independent of the tissue factor pathway, leading to a massive rise in thrombin generation at the platelet surface. **[52]**

High-dose rFVIIa can therefore compensate for a lack of factor VIII or factor IX through what has been described as a bypass effect,which explains its efficacy in treating patients with hemophilia with inhibitors. This may also explain the effectiveness of rFVIIa in treatment of bleeding episodes in patients with platelet function disorders. **[53]** Because of its a short half-life (2.7 hour), rFVIIa has to be given as 2-hourly boluses or as a continuous infusion. Which of these regimens is better is still a matter of debate. Some studies have shown that continuous infusions result in a satisfactory haemostatic response**.[54]**However, others have reported that continuous infusions can be ineffective.[**55**]

Despite these conflicting results, rFVIIa can be administered by continuous infusion as long as levels of factor VII:C of 30–40 IU/ ml are achieved in the immediate postoperative period and levels are maintained above 10 IU /ml thereafter.[**56**]

Recombinant factor VIIa is a pan-haemostatic agent and as such can be used in treating bleeding episodes in other disorders of haemostasis, such as factor VII deficiency, quantitative and qualitative platelet disorders, acquired von Willebrand disease, uraemia and liver disease.[**57**]

The use of rFVIIa in patients without pre-existing haemostatic defect is currently under intense investigation. Preliminary results suggest that it can be used safely and effectively to control life-threatening bleeding in surgery and trauma, when all other measures have failed. It can also be used to reduce blood loss and transfusion requirements in

elective surgical procedures associated with excessive bleeding. It should be noted, however, that rFVIIa has not been approved for use in any of these applications.[**47**]

The mechanism of action of rFVIIa suggests enhancement of haemostasis limited to the site of injury without systemic activation of the coagulation cascade. Therefore, the use of the drug in trauma patients suffering uncontrolled hemorrhage appears to be rational. Martinowitz and colleagues93 reported the use of rFVIIa in seven massively bleeding, multitransfused, and coagulopathic trauma patients after failure of conventional measures to achieve haemostasis. Administration of rFVIIa in a dose range of 120–212 mg /kg resulted in cessation of the diffuse bleeding, with significant reduction in blood transfusion requirements, and shortening of prothrombin time and activated partial thromboplastin time. The results of this report suggest that rFVIIa may prove to be of value as an adjunctive haemostatic agent in trauma patients. In other case reports of patients without preexistent coagulation disorders, who bled profusely during various surgical procedures, the use of rFVIIa was reported to stop bleeding very efficiently.[**58**]

Recombinant factor VIIa has also been investigated in the elective settings of cardiac, prostatic and liver transplant surgery. Al-Douri and colleagues2 evaluated the role of rFVIIa in five patients (one child aged 2.5 year and four adults) undergoing surgical procedures including arterial switch, closure of atrial septal defect, and mitral valve replacement with tricuspid valve repair. Haemostasis was achieved with a single dose (30 mg/ kg) of rFVIIa. The authors concluded that rFVIIa represents an effective and well-tolerated treatment for serious bleeding episodes both during cardiac surgery and postoperatively.[**47**]

Table (2): The advantages and disadvantages of the various haemostatic agents.[**47**]

Agent	Advantages	Disadvantages
Desmopressin	Useful in patients with mild haemophilia or type I von Willebrand's disease undergoing surgery. Can be used to treat or prevent bleeding in patients with congenital or acquired defects of platelet function, chronic liver disease and uraemia. Useful in treating patients with aspirin-induced platelet dysfunction undergoing cardiopulmonary bypass.	Available evidence does not support its use in haemostatically normal patients undergoing elective cardiac or non-cardiac surgical procedures. Reports of increased risk of postoperative myocardial infarction in patients undergoing coronary artery bypass grafting.
Epsilon-aminocaproic acid	Has been poorly evaluated in cardiac and non-cardiac surgery and adequate large randomized controlled trials are lacking. This makes it difficult to draw conclusions for or against its use in surgical patients.	
Tranexamic acid	Effective in reducing the need for blood transfusion in patients undergoing primary cardiac surgery, off-pump coronary surgery and thoracic aortic procedures. In cardiac surgery, it has not been effective. Effective in reducing blood loss in joint replacement operations and orthotopic liver transplantation.	in reducing blood loss in patients on aspirin and those undergoing repeat operations. Anecdotes suggesting an increased incidence of thromboembolic manifestations associated with its use. Inexpensive with adequate safety profile Concerns regarding renal toxicity if its use is continued postoperatively.
Nafamostat	Effective in reducing blood loss when used in orthotopic liver transplantation and cardiopulmonary bypass procedures.	No experience with its use in the UK, Europe or the USA.
Aprotinin	Has been consistently reported to reduce transfusion requirements in cardiac surgery. It is of particular benefit in patients taking aspirin, in patients with endocarditis, and in patients undergoing repeat operations , off-pump surgery or heart transplantation The only antifibrinolytic that has been associated with reduced mortality, reduced incidence of strokes and shorter hospital stay. Has been effective in reducing blood loss in major thoracic surgery, in major orthopedic surgery, and orthotopic liver transplantation.	Hypersensitivity reactions, particularly on re-exposure. Case reports of graft occlusion after cardiopulmonary bypass; other reports suggest an increased incidence of thromboembolic manifestations. Trend towards a mild to moderate increase in postoperative serum creatinine
Factor VIIa	Preliminary results suggest that it can be used safely and effectively to control life-threatening bleeding in surgery and trauma, when all other measures have failed. It can also be used to reduce blood loss in elective surgical procedures associated with excessive bleeding	Has not been approved for use as a haemostatic agent in patients without pre-existing bleeding disorders undergoing elective surgery. More clinical trials are awaited before definitive conclusions can be made about the safety and the exact role of this

		new drug in surgical patients. Case reports of myocardial infarction, cerebral ischemia, pulmonary embolism and deep-vein thrombosis.

Non-pharmacological management options

Radiologically aided arterial embolization

These techniques are becoming more widespread and successful cessation of bleeding can be achieved with embolization of bleeding arteries following angiographic imaging. The suitability of such manoeuvres needs to be assessed in each individual case and will also depend on availability of an interventional radiologist. The technique can be remarkably effective and may eliminate the need for surgical intervention, particularly in major obstetric haemorrhage.[**59**]

Cell salvage

The use of intra-operative cell salvage can be very effective at both reducing demand on allogeneic supplies and providing a readily available red cell supply in massive haemorrhage. National Institute of Health and Clinical Excellence (NICE) guidelines have also supported its use where large blood loss is experienced in obstetric haemorrhage and complex urological surgery such as radical prostatectomy. The indications for cell salvage are detailed in Blood Transfusion and the Anaesthetist – Intra-operative Cell Salvage[**59**].

Trauma call

A:patent airway&c/spine protection
B:ensure adequetebreathing,circulation,oxygenation
C:venous access 2 large bore cannulae;inspect for sourcesof bleeding
D:conduct GCS
E:commence hypothermia protocol

External long bones
CXR&PXR <10mins
DPA +/- FAST < 30mins

Interventions
Apply pressure
Splint long bones
Chest tubes
Pelvic sling
angiography

ABC TOOL
Penetrating mechanism
ED SEP <90mmhg
ED HR > 120tpm
Positive fast

Massive transfusion Trigger 7
ABC tool or 2 :
4units – 4hrs

Continue with 1ry & 2ry survey

Transfusion triggers
Platelets <75×10 g/l=1bag of plts
Platelets <50×10 g/l=2bag of plts
INR>1.5=2 bags FFP
INR>2.0=4 bags FFP
FIBRINOGEN <1.5g/l= 6bages of cryo
FIBRINOGEN <1.0g/l= 12bages of cryo
FIBRINOGEN <0.5/l= 18bages of cryo

Bolus 1 to 2 litres Warm crystalloid sol.

Minimize crystalloid

Remember it can take >30 mins to thaw FFP & Cryo

Commence RBCS O Negative

On release of MEP 1
Blood bark noffles
Heamatology register who will telephone the trauma team leader in ED on ext 24890 with the 1st coagulation sample results

Consider Novoseven
Inconsultation with haematology registrar
Inclusion
-Persistant uncontrolled hge
-Not managed by stabilization,surgical exploration or transfusion
Exclusion criteria
-Ph <7.15
-temp<34degrees

If theatre required urgently intiate trauma

Initiate MEP 1 BLOOD bank telephone
Commence documentation on the massive tranfussion sheet
MEP 1 contents
- 4units 0 –ve
- 2 units FFP
- 4 Units platelets
- Massive transfussion fluid balance

Continue resusitation based on clinical parameters and ongoing bleeding (ensure post administrationbloods have been taken and sent)

MEP PACK TWO
Blood bank telephone 27275 or 27276 and notify of patient location &clinical status
MEP 2 onwards contents
- 4units 0 –ve
- 4 units FFP
- 4 Units platelets
- Massive transfussion fluid balance sheet

Resuscitation endpoints
-Haemorrage control
-INR 1.5 or less
-Fibrinogen 1.5 or more
-Platelets >50 or >100 if critical structures at risk of bleeding
-PH >7.20
-SBP:80-90 mmhg
-Temperature >36 degrees

Continue resusitation based on clinical parameters and ongoing bleeding (ensure post administrationbloods have been taken and sent)

Release group specific

MEP PACK THREE

Fig.7:Protocol of mangemenat of massive blood loss [38]