Review Article

Massive transfusion and massive transfusion protocol

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ABSTRACT

Haemorrhage remains a major cause of potentially preventable deaths. Rapid transfusion of large volumes of blood products is required in patients with haemorrhagic shock which may lead to a unique set of complications. Recently, protocol based management of these patients using massive transfusion protocol have shown improved outcomes. This section discusses in detail both management and complications of massive blood transfusion.

Key words: Blood loss management, massive blood transfusion, massive transfusion protocol

INTRODUCTION

Massive blood loss is encountered in various situations like polytrauma, major surgeries, gastrointestinal bleeds, obstetric haemorrhage, etc. Timely recognition and efficient management are vital for successful outcomes after major blood loss. American College of Surgeons National Surgical Quality Improvement Program database over 3 years revealed very low incidence of massive transfusion. However, it was associated with high mortality as compared to patients without transfusion. Nonfatal complications such as respiratory and renal, were seen in more than 50% of patients when more than 5 units were transfused.[1] In an analysis of haemorrhage claims in the United States Anaesthesia Closed Claims Project database for claims between 1995 and 2011, the authors note that anaesthesia care was more often assessed as less than appropriate.[2] Anaesthesiologists and other acute care physicians should, therefore, be well versed in the current concepts in the management of massive blood loss and transfusion.

DEFINITION OF MASSIVE BLOOD TRANSFUSION

Various definitions of massive blood transfusion (MBT) have been published in the medical literature such as:[3-5]

- Replacement of one entire blood volume within 24 h
- Transfusion of >10 units of packed red blood cells (PRBCs) in 24 h
- Transfusion of >20 units of PRBCs in 24 h
- Transfusion of >4 units of PRBCs in 1 h when on-going need is foreseeable
- Replacement of 50% of total blood volume (TBV) within 3 h.

The definitions that use the period of 24 h are not useful during active management of blood loss. Furthermore, when used to identify MBT cases for observational studies, they dilute the data by selecting out early deaths. Therefore, the dynamic definitions, which identify rapid blood transfusions are better suited for use in day-to-day practice.

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Data regarding MBT in the paediatric population is scarce. Definitions of MBT suggested for use in children are transfusion of >50% TBV in 3 h, transfusion >100% TBV in 24 h or transfusion support to replace on-going blood loss of >10% TBV/min.[6]

PRINCIPLES OF MANAGEMENT OF MASSIVE BLOOD LOSS

Management of intravascular volume loss

a. This is a vital component of blood loss management. Physiologically, haemodynamic compensatory mechanisms maintain vital organ perfusion till about 30% TBV loss,[7] beyond which there is risk of critical hypoperfusion. Inadequate resuscitation at this stage leads to shock. Management of haemorrhagic shock is described elsewhere in this issue.
b. It is important to remember that overzealous resuscitation leading to high arterial and venous pressures may be deleterious as it may dislodge haemostatic clots and cause more bleeding.[8]

Management of loss of blood components

Blood component loss during massive blood loss is best managed by following the massive transfusion protocol (MTP). Mild to moderate blood loss can be managed with crystalloid or colloid infusions alone. However, with increasing loss, dilutional anaemia and later dilutional coagulopathy sets in. Also, plasma substitutes may have direct effects on the coagulation system particularly if used in volumes >1.5 L. In a study on surgical patients with normal coagulation factors, haemostatically critical levels of platelets ($50 \times 10^3/mm^3$), fibrinogen (1.0 g/L) and coagulation factor II, V and VII were reached at blood loss >200%, 150% and 200% respectively.[9-11] Therefore, it is generally recommended that replacement of blood components be guided by laboratory tests.[7] However in situations of large blood losses, the laboratory test based approach for replacement of coagulation factors may lead to a delay in the recognition and treatment of a rapidly developing coagulopathy as turnaround times for most laboratory tests is long. This may lead to catastrophic bleeding. A protocol based empirical replacement of coagulation factors is, therefore, recommended in massive blood losses.

Special considerations

a. Trauma: Acute coagulopathy of trauma shock is caused by a combination of tissue injury and shock, and may occur without significant fluid administration, clotting factor depletion or hypothermia[12,13]
b. Coagulopathy during cardio pulmonary bypass (CPB): Heparin given before CPB and hypothermia lead to platelet dysfunction that has been shown to be a major cause for bleeding in patients on CPB.[14,15] Extensive surgical trauma, prolonged blood contact with the CPB circuit, hypothermia and high doses of heparin lead to dysfunction of the coagulation and inflammatory systems further worsening the postoperative coagulopathy. In these cases, it is important to ensure adequate reversal of anticoagulants like heparin
c. Postpartum haemorrhage: Recent studies suggest that acquired fibrinogen deficiency may be the major coagulation abnormality associated with obstetric bleeding[16] which may be compounded by dilutional coagulopathy and hyperfibrinolysis.[17]

WHAT IS MASSIVE TRANSFUSION PROTOCOL?

With better understanding of the pathophysiology of haemorrhagic shock, resuscitation of patients with massive haemorrhage has advanced from reactive, supportive treatment with crystalloid, PRBC, and laboratory report based use of coagulation factors, to use of proactive standardized protocols called MTPs. MTPs are designed to interrupt the lethal triad of acidosis, hypothermia and coagulopathy that develops with massive transfusion thereby improving outcome. MTP describes the process of management of blood transfusion requirements in major bleeding episodes, assisting the interactions of the treating clinicians and the blood bank and ensuring judicious use of blood and blood components. By developing locally agreed and specific guidelines that include clinical, laboratory, blood bank and logistic responses, clinicians can ensure effective management of massive blood loss and improve outcome.

Rationale for massive transfusion protocol

Physicians involved in managing war injuries noticed that early administration of fresh frozen plasma (FFP) during massive transfusion decreased coagulopathy and improved survival in patients. Aggressive management of injury-associated coagulopathy has been promoted in recent years in massive blood loss. Studies have shown improved survival using higher ratio of FFP to RBC transfusion as compared to the conventional approach.[18-20] Transfusing fresh whole

blood would seem ideal but the time required to conduct safety tests on blood is long enough to cause significant depletion of coagulation factors. Therefore, administering RBCs, coagulation factors and platelets together maintains the physiological constitution of blood and prevents deficits of one or more constituents.

Massive transfusion protocols are activated by a clinician in response to massive bleeding. Generally this is activated after transfusion of 4-10 units. MTPs have a predefined ratio of RBCs, FFP/cryoprecipitate and platelets units (random donor platelets) in each pack (e.g. 1:1:1 or 2:1:1 ratio) for transfusion.[21,22] Once the patient is in the protocol, the blood bank ensures rapid and timely delivery of all blood components together to facilitate resuscitation. This reduces dependency on laboratory testing during the acute resuscitation phase and decreases the need for communication between the blood bank, laboratory and physician.

Limitations of massive transfusion protocols

1. Not standardised: The trigger for initiating the protocol as well as the optimum ratio of RBC: FFP: Platelets is controversial. Therefore practice varies from centre to centre.
2. Wastage: If MTP is triggered for a nonmassive blood loss situation, it may lead to wastage of blood products.

Other haemostatic/blood replacement strategies

1. Activated factor VII: The role of recombinant activated factor VII (rFVIIa) to manage uncontrolled bleeding is unclear. However, it can be considered as a rescue therapy in patients with life-threatening bleeding that is unresponsive to standard haemostatic therapy. When rFVIIa is used, the recommended dose is 200 μg/kg initially followed by repeat dose of 100 μg/kg at 1 h and 3 h[23]
2. Antifibrinolytic agents: Drugs like tranexemic acid may be useful in bleeding complicated by fibrinolysis such as cardiac surgery, prostatectomy etc.[24] Early administration of tranexamic acid in bleeding trauma patients has been shown to significantly reduce mortality[25,26]
3. Cell salvage: Can be extremely useful in unanticipated blood loss and in patients with rare blood groups. This strategy is generally reserved for massive blood loss in operation theatres as asepsis can be maintained easily. However, the relative contra indications such as a possibility of contamination with infected material and malignant cells should be considered.[27]

COMPLICATIONS OF MASSIVE TRANSFUSION

Immediate

Problems secondary to volume resuscitation

a. Inadequate resuscitation: Hypoperfusion leads to lactic acidosis, systemic inflammatory response syndrome (SIRS), disseminated intravascular coagulation and multiorgan dysfunction. It also increases the expression of thrombomodulin on endothelium, which then complexes with thrombin, which in turn leads to a reduced amount of thrombin available to produce fibrin and increases the circulating concentrations of anticoagulant activated protein C, which worsens the coagulopathy
b. Overzealous resuscitation
   i. Transfusion Associated Circulatory Overload: This is a well-known condition that occurs due to rapid transfusion of blood or blood products. Though this is seen commonly in elderly patients, small children and patients with compromised left ventricular function, it can also be seen in patients requiring massive transfusion. In patients with haemorrhagic shock, crystalloids and colloids are used for initial resuscitation. When blood and blood products become available, patients are transfused with required components that may then lead to circulatory overload.
   ii. Interstitial oedema due to increased hydrostatic pressure which may lead to abdominal compartment syndrome.

Dilutional problems

a. Dilutional coagulopathy: During haemorrhagic shock, there is fluid shift from the interstitial to the intravascular compartment that leads to dilution of the coagulation factors. This is further accentuated when the lost blood is replaced with coagulation factor deficient fluids. Studies have also shown that infusion of colloids and crystalloids induce coagulopathy to a greater extent than that explained by simple dilution.[28-30]
b. Low colloid oncotic pressure giving rise to interstitial edema.

Problems related to transfusion of large volume of stored blood

a. Citrate toxicity: 80 ml of citrate phosphate dextrose adenine solution present in each blood bag contains approximately 3 g citrate. A healthy adult can metabolise this load in 5 min.[31] However, hypoperfusion or hypothermia associated with massive blood loss can decrease this rate of metabolism leading to citrate toxicity. Unmetabolised citrate can then lead to hypocalcaemia, hypomagnesemia and worsen the acidosis. Hypocalcaemia can lead to myocardial depression that manifests earlier than hypocalcaemic coagulopathy. Hypotension not responding to fluids should alert the physician to this complication. Calcium supplementation is thus required in most cases of MBT.

b. Hyperkalaemia: Potassium concentrations in PRBCs can range from 7 to 77 mEq/L depending on age of stored blood.[32] Development of hyperkalaemia will depend on the underlying renal function, severity of tissue injury and rate of transfusion. At transfusion rates exceeding 100-150 ml/min, transient hyperkalaemia is frequently seen.[33] Also, acidosis secondary to hypoperfusion may worsen hyperkalaemia. Cardiac effects of hyperkalaemia are accentuated by hypocalcaemia.

c. Hypothermia: Factors contributing to hypothermia include infusion of cold fluids and blood and blood products, opening of coelomic cavities and decreased heat production. Hypothermia leads to decreased citrate metabolism and drug clearance and more importantly, contributes to the development of coagulopathy. Slowing of enzyme activity and decreased platelet function individually have been shown to contribute to hypothermic coagulopathy at core temperatures below 34°C.[34] Coagulopathy due to hypothermia is not reflected in laboratory tests as the samples are warmed during processing.

d. Hypomagnesemia: Citrate also binds to magnesium and can lead to hypomagnesaemia which can further accentuate effects of hypocalcaemia. Infusion of large amounts of magnesium poor fluid can also contribute to hypomagnesemia.

e. Acidosis: After 2 weeks of storage, PRBCs have a pH below 7.0, and each unit has an acid load of approximately 6 mEq. One of these mEq of acid comes from the fact that PRBCs are made from venous blood with a starting pH of 7.35, a second mEq is acquired in buffering the citric acid in the anticoagulant, and 4 mEqs are generated by glycolysis during PRBC storage.[35] Acidosis directly reduces activity of both extrinsic and intrinsic coagulation pathways. A pH decrease from 7.4 to 7.0 reduces the activity of FVIIa and FVIIa/TF by over 90% and 60% respectively.[36]

Late complications

1. Respiratory failure
   Transfusion related acute lung injury (TRALI): The risk of TRALI increases with the number of allogenic blood and blood products transfused. The exact pathologic mechanisms of TRALI have not been clearly understood and both immunologic and nonimmunologic mechanisms have been suggested
2. SIRS
3. Sepsis
4. Thrombotic complications.

Preparation for massive bleeding

- Large bore intravenous (IV) access: Two peripheral IV (14/16 gauge) cannulae or special wide bore cannulae (insertion sheath) can be sited in neck veins such as the internal jugular vein. In emergency situations, canulation of external jugular vein may be considered
- Warming devices: In-line fluid warmers and surface warmers
- Continuous core temperature monitoring
- Invasive arterial pressure monitoring
- Adequate amount of colloid (gelatins), crystalloid, infusion sets and IV calcium preparations
- Communication with blood bank about emerging massive blood loss situation
- Adequate manpower for sending samples for investigations and getting blood and blood products
- Point-of-care testing is highly desirable: Arterial blood gas (ABG) and thromboelastograph (TEG). ABG with haemoglobin (Hb), electrolyte and lactate levels, repeated hourly, are useful in directing therapy
- Rapid infusion pumps or pressure bags to speed the fluid infusion rate
- Postoperative intensive care: Mechanical ventilation and continuous haemodynamic monitoring are usually required due to occurrence of circulatory overload and haemodynamic/biochemical instability.

Monitoring

Clinical monitoring: Electrocardiogram, capnometry, pulse oximetry, arterial blood pressure, core temperature, and urine output.

Invasive arterial pressure: Invasive arterial pressure measurement allows beat-to-beat pressure measurement and has greater accuracy than cuff based measurements in low flow conditions. Also, the arterial catheter allows frequent arterial blood sampling which is useful in guiding therapy. Many modern haemodynamic monitors calculate pulse pressure variation which is a more specific indicator of volume responsiveness.

Role of central venous pressure monitoring: Central venous catheters, due to their length and high resistance, allow inferior flow rates than wide bore cannulae. However, they are useful for assessment of the haemodynamic status, administration of vasoactive agents and blood sampling.

Laboratory monitoring: Laboratory values should be obtained frequently. Recommended lab tests include Hb, platelet count, prothrombin time, partial thromboplastin time (PTT), fibrinogen, potassium, ionized calcium, ABG for acid base status and central venous oxygen saturation/lactate as an indicator of tissue hypoperfusion.

Limitations of conventional laboratory testing: The time lag between collection of samples and obtaining the reports is a serious limitation in their utility during rapid on-going blood loss.

Role of point of care coagulation testing

Coagulation tests usually have long processing times and may not be helpful in guiding therapy in a rapid evolving blood loss situation. However, results may be useful later to assess how the case developed. Thromboelastography (TEG) is test of the visco elastic properties of blood that examines the entire haemostatic system including platelet function and fibrinolytic system and is particularly useful in complicated coagulopathies. Also, rapid availability of results helps in timely intervention.

Targets of resuscitation in massive blood loss

- Mean arterial pressure (MAP) around 60 mmHg, systolic arterial pressure 80-100 mmHg (in hypertensive patients one may need to target higher MAP)
- Hb 7-9 g/dl
- INR <1.5; activated PTT <42 s
- Fibrinogen >1.5-2 g/L
- Platelets >50 × 10^9/L
- pH 7.35-7.45
- Core temperature >35.0°C
- Base deficit <3.0/lactates <2 mEq/L.

Practical tips

1. Early recognition of massive blood loss and triggering MTP - prescribe blood and blood products early to allow for delivery time lag and thawing time (30 min for FFP)
2. Collect blood sample for cross match early as colloids may interfere with cross matching (mainly dextrans by coating RBC surface)
3. Inotrope/vasopressor drugs should only be used in a blood loss scenario during severe hypotension to avoid critical hypoperfusion and to buy time for fluid resuscitation. They should be stopped as soon as volume deficits are replaced, and a safe blood pressure is achieved.
4. Do not exceed recommended maximum doses of colloid. Also use of starch based colloid solutions in large volumes in a haemodynamically critical patient is controversial in view of evidence of renal dysfunction associated with their use in intensive care unit.[37]

SUMMARY

Management of massive loss requires a quick concerted team effort by many medical and paramedical members. Understanding the complex pathophysiology of massive blood loss and its replacement is crucial to a successful outcome. Recent evidence supports early use of coagulation factors to improve outcome. Indian hospitals should formulate MTPs suited to their need and resources to improve survival in massive blood loss.

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