Review of Blood Transfusion Strategies among Trauma Patients

Sumit Vishwakarma, Garima Aggarwal and Arulselvi Subramanian*

Departments of Lab Medicine & Blood Bank, Jai Prakash Narayan Apex Trauma centre, AIIMS, New Delhi

Abstract: *Introduction:* Trauma is the third most common cause of mortality worldwide and leading cause of death in the age group 1 to 44 years. Among those trauma patients, major hemorrhage is responsible for 30 to 40% of mortality, despite the fact that it could be preventable and reversible. The ideal resuscitation strategy for trauma patients remains a topic of ongoing debate. Transfusion services stress trauma centers with demands for strict accountability for individual blood component units and adherence to indications in a clinical field where research has been difficult and guidance opinion-based. New data suggest that the most severely injured patients arrive at the trauma center already coagulopathic and these patients benefit from prompt specific and corrective treatment. At present, no consensus has been reached on ideal fluid for early resuscitation and on the threshold for blood product transfusions. This review article provides a brief overview of recent advances in trauma induced hematological complications, role of pathologist in managing them and subsequent complicating issues. Thereby, covering the widest possible body of literature.

Aims and objectives: In this review we address ongoing resuscitation strategies along with potential complications in management of the trauma patients. This review also assesses the still ongoing, controversial debate of the best fit treatment options. This research is clarifying trauma system requirements for new blood products and blood-product usage patterns, but the inability to obtain informed consent from severely injured patients remains an obstacle to further research.

Methods: We considered systematic reviews identified through searches of Cochrane databases from inception to April 2015 and PubMed up to April 2015.

Results and Conclusions: Polytrauma patients with severe shock from haemorrhage and massive tissue injury present major challenges for management and resuscitation. Many of the current recommendations for damage control resuscitation remain controversial. A lack of large, randomized, control trials leaves most recommendations at the level of consensus and expert opinion. Ongoing trials and improvements in monitoring and resuscitation technologies will further influence how we manage these complex and challenging patients.

Keywords: Massive hemorrhage, Post injury coagulopathy, Thromboelastography, Damage control resuscitation, Transfusion protocols, Trauma center.

INTRODUCTION

Trauma is defined as any mechanical damage to body caused by external force. It is one of the major cause of mortality all over the world. Trauma related deaths can be immediate occurring within minutes to hours and most of these patients are dead before they reach hospital, the major cause being neurological injury or massive bleed due to injury to major vessels. These account for around half of trauma related deaths. Another quarter of patients die during initial hours of post injury; they however usually have access to trauma care and avoiding mortality among these patients is the goal of modern trauma care. Rest of the mortality occurs late during the hospital care (1-2 weeks or more post injury) due to sepsis, multi organ failure or other comorbid conditions. There are different scores described in literature to categorize trauma patients although none is ideal [1]. There should be a basic approach to trauma patient in terms of assessing airway, breathing, circulation, disability and exposure to rule out any other injury wound. Our discussion will be limited to the circulatory part *i.e*. discussing the trauma related hematological changes, their detection, role of pathologist in management and subsequent care.

PHYSIOLOGICAL CHANGES IN TRAUMA PATIENTS

Hemorrhage in trauma patients lead to decreased vital organ perfusion which is compensated by peripheral vasoconstriction, release of epinephrine and activation of rennin angiotensin pathway in an attempt to restore perfusion. There is activation of coagulation pathway to restrict blood loss; side by side there is activation of fibrinolytic pathway, shift of extracellular fluid in the circulation thereby diluting coagulation factors and thus contributing to trauma induced coagulopathy. Traumatic bleeding if not corrected timely an adequately by intravenous fluids and blood products lead to anemia thus contributing further to cardiopulmonary stress [1].

An initial workup should include complete blood count, blood gas analysis, prothrombin time, partial thromboplastin time, fibrinogen level, cross matching and serum electrolytes.

*Address correspondence to this author at the Departments of Lab Medicine & Blood Bank, Jai Prakash Narayan Apex Trauma centre, AIIMS, New Delhi; Tel: 011-26731169; Fax: 011-26106826; E-mal: arulselvi.jpnatc@gmail.com

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Adults who loose < 20% of total blood volume do well without blood transfusion provided blood volume is maintained by administration of crystalloids. Massive hemorrhage as defined as transfusion of more than 10 U of RBCs in 24 hour period is common cause of immediate and early deaths in trauma patients. It is in these patients the role of blood component support emerges. There are several protocols followed by transfusion services to provide quick and efficient blood product packages to these patients. However, risk of transfusion and its benefits to patient should always be weighed. RBCs should be used along with intravenous fluids to correct volume depletion and anemia [2].

Administering blood should be initiated at the scene of the accident, thus avoiding the rapid administration of i/v fluids (filler fluid) that has been traditionally promoted by the advanced trauma life support (ATLS) guidelines. This involves giving two liters of crystalloids and continuing with packed red blood cells (PRBCs) and fresh frozen plasma (FFP) if there was transient or no response, with the aim of achieving normotension. Nevertheless, it has been noted that the patients receiving more preoperative fluid *i.e*., standard fluid resuscitation (SFR) have higher intraoperative and overall mortality rate than the restricted fluid resuscitation (RFR). The higher mortality rate is attributed to the effect of large volume of fluids in diluting clotting factors and lowering blood viscosity and the raising blood pressure [3]. Limited attempts to restore blood pressure improve cardiac output, tissue perfusion as well as survival while attempts to restore normal tension with crystalloid only results in increased hemorrhage and higher mortality [4].

Morrison *et al*. demonstrated the lower requirement of fluid and blood product transfusion, lower postoperative mortality and reduced postoperative bleeding and less frequent and less severe coagulopathy as evidenced by INR measurements in the group managed by hypotensive resuscitation [5].

However, same was not found by Dutton *et al*, [6] who found equal mortality rates amongst patients whose fluid therapy was targeted to achieve systolic Blood pressure (SBP) > 100 mmHg and 70 mmHg respectively.

This basic dissimilarity in the hemodynamic response between controlled hemorrhagic shock (CHS) in which the bleeding source has been occluded, and uncontrolled hemorrhagic shock (UCHS) in which bleeding has temporarily stopped because of hypotension, vasoconstriction, and thrombus formation also constitutes the basis for fluid resuscitation [7].

Recent data has shown improvement in clinical outcome when ratio of blood components transfused were similar to whole blood. Subsequent reports, primarily in the military literature, further support a component therapy transfusion in ratios of 1 U RBC/1 U plasma/1 random donor unit of platelets. However, these suffer from survivorship bias and lack adjustment for confounding variables such as injury severity [8]. Civilian trauma studies have also evaluated the impact of more aggressive ratios and noted an association with improved survival. Similar to the military data, such studies also support using a more aggressive RBC/plasma ratio, reporting a significant reduction in 30-day mortality as compared with those that received less plasma. This was independent of age and trauma related injury severity score, which by themselves were independent predictors of mortality [9].

PACKED RED BLOOD CELLS

Use of RBC transfusion at a hemoglobin level above 10 mg/dl is not advocated by various transfusion policies ; transfusion is recommended if hemoglobin level falls below 6 mg/dl [10]. In addition, there is an extensive acceptance of a target value ranging between 7 and 10 mg/dl post transfusion [11]. A recent comparison between platelet concentrates (PCs) and fresh whole blood did not provide a major advantage of whole blood versus stored thrombocytes [12]. The risk for transmission of infectious diseases or microorganisms is clearly higher when fresh whole blood is transfused. So, taken together, transfusion of fresh whole blood seems to be a reliable strategy in the military, but not in the civilian setting [13].

GROUP O RED CELLS

In trauma patients with massive bleeding, it is imperative to transfuse blood immediately, and no blood bank testing should be attempted before emergency transfusion. As group “O” red cells are considered universal donar, risk of transfusing group O “uncrossmatched” red cells is much lower than the risk of patient’s death if blood transfusion is delayed. If a patient is to be given uncrossmatched blood, a specimen of the patient’s blood should be obtained prior to transfusion so that typing and screening can be performed while the transfusion is proceeding [2]. Use of uncross matched group O red cells in a trauma referral unit (TRU) led to decreased survival in patients who were increasingly transfused with unmatched group O red cells. The safety of using uncross matched red cells is occasionally questioned because of the possibility of group O donors having high titers of anti-A

or anti-B. While reactions have been reported, the incidence and severity of such complications is less than that of not receiving blood or the risk of receiving red cells of the wrong ABO type in emergency situations [14].

AUTO-TRANSFUSION

Autologous blood donation is blood donated by a patient, intended for transfusion back into the same patient. It may reduce or even eliminate the need for allogeneic blood. In autologous blood cell salvage, blood lost during or after a surgical procedure is salvaged for reinfusion. Use of an auto-transfusion device (such as a cell-saver) was found to be well tolerated and effective in patients with intra-abdominal contamination and hemoperitoneum. Smith and colleagues [15] recently noted that intraoperative blood salvage is not only well tolerated but that application of such devices is associated with a marked decrease in the use of banked blood.

In a randomized controlled trial there was no difference in the intra operative blood salvage group compared to controls in regards to postoperative sepsis, survival, coagulopathy, and requirement for clotting factors. To save valuable banked blood, those centers with the capability to provide this adjunct 'around-the-clock' should strongly consider the use of this important tool in the management of the exsanguinating patients [16].

TYPES OF INFUSED FLUIDS

Fluids are the first-line therapeutic approach used for resuscitation. In bleeding trauma patients, aggressive fluid administration aimed at restoring intravascular blood volume is considered as main concept of resuscitation. But, by increasing hydrostatic pressure on the clots, an aggravation of hypothermia, and a further dilution of coagulation factors may contribute to further blood loss.

Crystalloids

Ringer lactate solution is the most common available and used balanced salt solution for fluid resuscitation in hemorrhagic shock. It is considered as safe as it equilibrates rapidly throughout the extracellular compartment, restoring the extracellular fluid deficit associated with blood loss. Rhee *et al.* [17] found that solution increases neutrophil superoxide burst activity and increased neutrophil adherence. It has been shown that aggressive crystalloid resuscitation was followed by increased cytokine activation including IL-1, IL-6, and TNF [18].

The main benefit of ringer lactate solution is that it act as a source of bicarbonate due to metabolism of lactate to CO_2 and H_2O; and in contrast to bicarbonate, ringer lactate solution does not precipitate calcium when it is added to intravenous fluids. Crystalloid solutions are relatively inexpensive also.

Colloid Solutions

The use of colloid solutions for treatment of hemorrhagic shock has been advocated because it tends to remain in the intravascular compartment. Several colloid solutions including human albumin, hydroxyl ethyl starch (HES) and dextran were studied in clinical practice. As colloid solutions remain mainly in the intravascular compartment, a lower total volume of resuscitative fluid is required to attain hemodynamic stability compared to crystalloid solutions. However, colloid solutions are more expensive, may bind and decrease serum ionized calcium, decrease circulating levels of immunoglobulines, and may further compromise the extracellular fluid volume deficit rather than restoring it. Crystalloid and colloid fluid resuscitation have been compared by many experimental and clinical studies [19]. There is no clinical evidence that appropriate resuscitation with balanced salt solution is associated with any harmful effects on pulmonary function when guided by hemodynamic parameters [20]. Although colloid solutions do produce transiently greater intravascular expansion per unit compared to crystalloid solutions, no protective effect of colloid solutions on post-resuscitation pulmonary function was demonstrated; some concerns about the influence of colloids on coagulation, renal failure, and pruritus have been reported [21].

Because of a major concern with regard to resuscitation of hemorrhage in the military setting where considerable weight and volume of crystalloid solutions must be transported in the field sometimes on the back of the medical professionals, colloid solutions are recommended in military scenarios. This results in an inadequate bulk of the ringer's lactate solution that is transported to the frontline and thus compromises the resuscitation phase in forward areas of deployment.

Hypertonic Solutions

Clinical and experimental studies showed that a small volume of hypertonic saline (5 ml/kg NaCl 7.5%)

with or without dextran can be an effective initial resuscitation solution. Hypertonic solutions improve micro vascular flow, control intracranial pressure, and stabilize arterial pressure and cardiac output with small-volume infusion, with no deleterious effects on immune functions [22].

Trauma Induced Coagulopathy

This is an important issue concerning physicians as well as pathologists. As already discussed injury leads to simultaneous activation of coagulation and fibrinolytic pathway. Activation of thrombin leads to activation of thrombomodulin and subsequent activation and consumption of protein C, however this occurs in patient with severe injury and hypoperfusion. Platelet dysfunction also plays a role. Other complication of trauma like acidosis and hypothermia also contribute to TIC. Meng *et al* [23] reported the effect of acidosis on coagulation cascade by measuring the activity of recombinant factor VIIa on phospholipids and platelets. When pH was reduced from 7.4 to 7.0, activity of these parameters decreased by 90%. Animal studies by Martini *et al* [24] showed that acidosis reduced fibrinogen concentration to 66% ± 2%, decreased platelet counts to 49% ± 4%, and decreased thrombin generation to 60% ± 4%. PT and PTT were found to be prolonged by about 20% due to acidosis. Acidosis correction mainly involves restoration of the circulation to maintain tissue perfusion. Apart from these, resuscitation measures in from of infusion of fluids and blood products leads to dilutional coagulopathy.

Currently, there are no accurate methods to assess acute trauma coagulopathy so the early empirical transfusion of blood and clotting factors are considered as best current treatment of coagulopathy [25]. Presumably, the extent of injury is great enough in these patients to lead to massive consumption of coagulation factors, either directly or through activation of the protein C pathway. The prevalence of an abnormal PT expressed as an international normalization ratio (INR), have been shown to increase from 5 to 45% and above rising side by side with the injury severity score from 5–9. However, the mortality rate increased from less than 1% for moderate injury and normal INR to more than 80% for severe injury and INR of 2.2 or greater. Abnormalities of other coagulation tests, such as the activated partial thromboplastin time, the fibrinogen concentration and the platelet count are less frequent but associated with major increases in mortality [26].

Monitoring of Coagulation

Usual diagnostic parameters such as prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT) can fail in predicting trauma-induced coagulopathy or perioperative bleeding complications precisely. These coagulation tests cannot recognize disturbances of the primary hemostasis (*e.g*. platelet dysfunction) and condition of hyperfibrinolysis. In addition the turn-around time of these tests is calculated to be between 30 and 90 min. Establishment of a 'guide' by a set novel biomarkers and/or easily applicable functional assays which allows for decision-making within reasonable time (*i.e*. 10–15 min) is an important aim of research in the field of transfusion and coagulation management. Monitoring by Rotational elastometer (ROTEM) or Thromboelastography (TEG) can be a promising approach. In a recent Cochrane analysis, 6 studies were identified which compared clinical judgment and standard laboratory tests or both in the adult cardiac surgery and liver transplantation setting [24-32]. These research could not found any beneficial effect of TEG or ROTEM on patient survival but they found a positive effects in pre defined outcomes such as reduced bleeding and reduced proportion of patients requiring transfusion of platelets or plasma to save the cost. Additionally, there were no negative effects or adverse events by the application of this Point of care (POC) technology. The effects of TEG driven therapy need a thorough investigation [28].

TREATMENT OF TRAUMA INDUCED COAGULO-PATHY

FFP

Due to dilution, consumption, and inhibition of coagulation any major blood loss leads to a hypocoagulable state. There is increasing number of evidence that early and more aggressive replacement of clotting factors reduces mortality and decreases transfusion volume [29]. Early standard use of FFP and PRBC has been shown rather to prevent than to treat a severe dilutional coagulopathy and might contribute to an improved survival. However, in patients with already clinically relevant factor deficiencies (<50% of activity), FFP might not be sufficient to restore coagulatory activity immediately. Furthermore, such a strategy would result in a high risk of Transfusion associated circulatory overload (TACO). Ho and colleagues [30] through their mathematical model for FFP transfusion strategies have calculated that 1–1.5 units of FFP must be given per unit of PRBC just to correct the dilutional component of coagulation alone.

Fibrinogen

Massive bleeding leads to loss, consumption, and dilution (by volume therapy) of coagulation factors. The first factor falling below a critical level is fibrinogen. Hiippala *et al* [31] showed that critical threshold was suspected at a level below 100 mg/dl and it was still recommended as a trigger for intervention in a European Guideline in 2007 [32]. Colloids interfere with the measurement of fibrinogen and should always be taken into account [33]. FFP is not suitable for a rapid increase in already reduced fibrinogen plasma levels.

Cryoprecipitate

Cryoprecipitate is a preparation rich in fibrinogen, factor VIII, XIII, von Willebrand factor, and fibronectin and has been used for therapy of hypofibrinogenemia. Typical dose of cryoprecipitate of one unit per 5-10 kg body weight is expected to raise fibrinogen level by around 70 mg/dl. Murthi *et al* used increasing amounts of cryoprecipitate in one very specific clinical situation: the patient with profound, ongoing hemorrhage, severe acidosis and established coagulopathy. This is the patient in whom efforts to prevent coagulopathy by the early use of plasma have failed, either because of overwhelming anatomic injury and profound shock (*e.g*., a stab wound to the heart) or pre-existing coagulation defects (*e.g*., end-stage cirrhosis). In these circumstances, the concentration of critical clotting factors in plasma is too dilute to reverse coagulopathy before the patient succumbs to hemorrhagic shock [14].

Prothrombin Complex Concentrate

The prothrombin complex concentrate (PCC) contains vitamin K-dependent coagulation factors II, VII, IX and X, which are essential for the generation of thrombin and natural anticoagulants C and S. It is extensively used for the therapy of inherited coagulation defects or the reversal of vitamin K antagonists [34].

Factor XIII

Hemorrhages as well as coagulopathy have been shown to cause acquired factor XIII deficiency. Factor XIII is used to stabilize the clot by forming covalent bonds between fibrin monomers and by cross-linking alpha-2 antiplasmin, fibrinogen, fibronectin, collagen and other proteins to enhance the mechanical strength of the fibrin clot and protect the clot from proteolytic degradation [35]. A decreased factor XIII activity leads to reduced clot firmness in TEG.

Hyperfibrinolysis and Inhibition

All injuries or major surgery might lead to hyperfibrinolysis, especially if organs with an increased level of plasminogen activators are involved [36]. Plasminogen activators are released from hypoxic endothelial cells, and plasminogen activator inhibitors are proteolysed by antigen-presenting cells. The gold standard test for the diagnosis of hyperfibrinolysis is the euglobulin lysis time, however the test requires 3 hours and is thus not feasible in the acute situation. The ROTEM platform is based on the principles of TEG and has becomes more and more established POC method for the detection of hyperfibrinolysis, although it does not have a very high sensitivity.

AB or Low-Titer A Plasma

The recognition of the acute coagulopathy of trauma and the dangers of massive use of crystalloid fluids in resuscitation has led to the suggestion that the prophylactic administration of plasma along with RBCs for initial resuscitation is appropriate in a small number of the most severely injured patients identified on the basis of rapid ongoing bleeding. Almost one half of such patients present to the hospital with deranged INR that would be good enough reason to transfuse plasma according to conventional transfusion guidelines. The core of damage-control resuscitation is beginning resuscitation with a 1:1 ratio of plasma to red cells in additive solution. This concept when implemented in hospitals in Baghdad and Iraq in treating massively injured patients markedly reduced coagulopathic bleeding, allowing surgeons to operate in less blood-obscured field. It also reduced tissue swelling and organ failure seen postoperatively. When studied retrospectively; there was a reduction in mortality from 66 to 19% in massively injured patients. A group of academic trauma centers have now confirmed this marked improvement in injury mortality in retrospective reviews of their own experience with massive transfusion in a combined series of more than 400 patients [37]. The belief that the most severely injured trauma patients should be resuscitated at earliest with a mix of red cells and plasma resembling whole blood is gaining wide acceptance, even though the optimal proportions of RBCs to plasma has not yet been defined [38].

Platelets

During acute blood loss, bone marrow and spleen release platelets into the circulation, and thereby

delaying thrombocytopenia. After transfusion, reverse happens: 60–70% of transfused platelets appear transiently in the peripheral blood over few days and rest fill up the platelet pool. Also an increased ratio of platelet concentrate (PC) to PRBCs increase survival by 30 days in trauma patients [39].

Due to progress in noninvasive cardiovascular procedures, there are an increasing number of patients receiving anticoagulatory therapy mainly targeting platelets, *e.g*. acetyl salicylic acid or glycoprotein IIb/IIIa inhibitors. In these patients, platelet transfusions are strongly advised in case of active bleeding even at higher platelet counts [40]. However, a purely prophylactic administration or a continuation after bleeding has stopped should be avoided as this might increase the rate of thrombosis in these patients. Likewise, patients on vitamin K antagonists should receive 50 u/ kg PC (prothrombin complex) and 10 mg vitamin K intravenously. Early work on blood component resuscitation from the Harborview group in Seattle suggested that platelets were not a significant issue in resuscitation in hemorrhagic shock [41]. The fact that hypothermia do play a role in the coagulopathy of trauma and platelet function has led to the idea of preventing hypothermia during resuscitation which also provides sufficient time to obtain a platelet count and blood type prior to adding platelets to the early transfusion mix [42]. Old work on dilutional coagulopathy suggested that many patients required platelets after transfusion of two blood volumes. However, subsequent studies on seriously injured patients suggest that patients receiving platelets early have lower rates of coagulopathy and mortality [43].

Desmopressin

Desmopressin by stimulation of extra renal V2 receptors and mobilization of thrombocytes from the bone marrow, [44] leads to the release of factor VIII and von Willebrand factor from the endothelium. It has been used if the patient is suffering from uremia, hepatic disease, or on aspirin but the efficacy is limited and inconsistent. Development of hypertension is one of the major side effects. Tachyphylaxis may be seen in some cases, but can be avoided if application is limited to <24 h [45].

TRANSFUSION ASSOCIATED ISSUES AND ROLE OF LABORATORY

Blood Transfusion can be associated with certain complications like immunologic and nonimmunologic reaction and various infections.

A. Immunological reaction can be as following;

1. Alloimmunization to red cell antigens, HLA antigen, platelets specific antigens and neutrophil specific antigens. The risk of red cell alloimmunization has been estimated at 1.0% to 1.4% per unit transfused [2]. If Rh-D positive red cells or platelets are given to a woman of childbearing age, it may be possible to prevent alloimmunization with the administration of Rh immunoglobulin. If she is clinically stable and heavily exposed, it may even be appropriate to perform red cell exchange by apheresis before administration of Rh immunoglobulin [45]. If alloantibodies were detected in the initial antibody screen and ignored in an initial urgent or massive transfusion, the possibility of a delayed hemolytic transfusion reaction must be considered and the care team notified.

2. Hemolytic transfusion reactions due to development of antibodies capable of reacting with red cell antigens may lead to red cell destruction usually involving transfused rather recipient blood. These reaction can cause immediate (intravascular) or delayed transfusion reaction [2]. A review of fatal hemolytic reactions said 86% were caused by ABO incompatibility and of these 89% were caused by simple clerical error [47]. Patients with major hemolytic transfusion reactions should be assessed for possible presence of intravascular coagulation. Their renal functiontests, urinary haemosiderin or free hemoglobin should be detected. Demonstration of methmalbuminema, reduced serum haptoglobin or hyperbilirubinemia may provide supportive evidence. Delayed haemolytic transfusion reactions (DHTR) are generally mild and show extravascular haemolysis. If a DHTR is suspected, direct antiglobin test should be done and if positive, antibody should be eluted from the red cells and identified [2].

3. Febrile non hemolytic transfusion reactions (FNHTR) have been reported in patient receiving transfusion, ranging from 0.5% to 3.0%. This is attributed to alloimmunization to leukocytes and platelets antigens. HLA antibodies are most commonly found, followed by platelet-specific antibodies and granulocyte-specific antibodies. Cytokines derived from leucocytes which get accumulated during blood product storage especially platelet concentrates which are stored

at room temperature are another main reason behind pathogenesis of FNHTR. The complication can be avoided by use of leucoreduced red cells [2].

4. Transfusion related acute lung injury (TRALI)- is the most frightening adverse effect of blood transfusion. The incidence of TRALI is much lower (~1:10,000) than that of other adverse effects such as severe febrile or allergic reactions (~1%); however, TRALI is a life threatening complication with urgent need of mechanical ventilation in most cases [48]. Diagnosis of TRALI is based on acute lung injury within 6 hours of transfusion. Acute lung injury shows hypoxemia, bilateral chest infiltrate on X-ray and no evidence of circulatory overload. Its management involves supportive measures and hemodynamic monitoring [2]. It is mainly associated with transfusion of plasma extracted from female donors. This is supported by the fact that incidence of TRALI was significantly reduced since plasma from women after pregnancy and/or child birth were excluded from the donor pool to avoid the transmission of antibodies with specificity mainly against human neutrophil antigens (HNA) or human leukocyte antigens (HLA). A further reduction might also be reached by the use of lyophilized plasma [48].

5. Allergic transfusion reactions are commonly seen in 1% to 3% of transfusion recipient. Whole blood and plasma are more likely to cause them rather concentrated red cells. If these are not controlled by medication; use of product with reduced plasma content, washed RBC and IgA deficient blood product can be an alternative option [2].

6. Post transfusion purpura can cause life threatening thrombocytopenia 5 to 10 days after transfusion. The management includes high dose IVIG, corticosteroids or plasma exchange [2].

7. Transfusion related imunomodulatory effects (TRIM) - allogeneic blood transfusion results in the transfer of not only RBCs, but also significant amounts of potential immunoeffector cells, their products (cytokine) and various substances that may be seen by the host immune system as foreign antigens [2].

8. Transfusion associated graft versus host disease (GVHD) is seen due to viable immune competent T lymphocytes. High risk for GVHD are patients undergoing BMT, patients receiving granulocyte and HLA matched platelet transfusion, transfusion from blood relatives, congenital immunodeficiency and Hodgkin's lymphoma [2].

9. Microchimerism is the presence of a small number of cells that originate from another individual and are therefore genetically distinct from the cells of the host individual. This phenomenon may be related to certain types of autoimmune diseases. The trauma and transfusion groups at the University of California, Davis (CA, USA), have shown that transfused trauma patients have a significant incidence of at least a transient transfusion-related microchimerism that can range from 10 to more than 50% of population. It appears to have the potential to persist in approximately 5% of affected individual for as long as up to a period of decades [49]. Microchimerism appears to occur when donor and recipient have closely matched HLA alleles. At this point, there do not appear to be chronic immunologic consequences of this finding [50].

B. Non immunological adverse effects;

1. Transfusion associated circulatory overload (TACO) is seen due to transfusion of red cell preparations or plasma products. To prevent these reactions transfusion should be administered slowly at the rate of 1 to 2ml blood per Kg of body weight per hour in close observation.

2. Massive transfusion may cause metabolic effects because stored blood differs in its composition from the circulating blood in the body. The elevated potassium content of stored red cells rarely leads to hyperkalemia but it is a risk in the presence of renal failure, shock with acidosis or hemolysis. Plasma contains increased citrate which may leads to hypocalcemia. Hypothermia may occur specially in neonates and elderly or particularly sensitive to these reactions. It may leads to arrhythmia and may interfere in platelets functions and clotting. Dilution coagulopathy may leads to abnormal PT, APTT and thrombocytopenia.

C. Currently the blood transfusions can roughly be categorized as noninfectious because transfusion-transmitted infections by HBV, HCV or HIV are actually very rare events as proved by the German Hemovigilance System [43]. In 1999,nucleic acid testing (NAT) for HIV and HCV RNA was added to blood donor screening. Infectious disease testing usually involves screening for Hepatitis B, hepatitis C, HIV-1/2, HTLV I/II, and syphilis. Other infections which can circulate in the blood of an apparently healthy donor are hepatitis A, delta virus, west nile virus, cytomegalo virus, dengue virus, parasites including malaria, babesia and trypanosome cruzi, variant of Creutzfeldt-Jakob disease and bacterial contamination.

Pathogen reduction technology

Donor screening and testing cannot completely eliminate the possibility of transfusion transmitted infections. Pathogen reduction technology for transferable blood component is a technique which should ideally inactivate residual pathogens without adversely affecting the functions, toxicity or immunogenicity of the blood components. Most commercial plasma derivatives are treated with heat and /or organic solvents and detergents and cellular blood components are added with additives that bind to and damage DNA of residual pathogens. There is concern that DNA altering agents can cause long term toxicity in transfusion recipient, requiring further work in this area [2].

LIMITING BLOOD PRODUCT EXPOSURE

The Transfusion Requirements in Critical Care trial showed that hemodynamically stable intensive care patients, including many trauma patients did not need red cell transfusion and neither had they appeared to benefit from it. [52] Many retrospective studies suggest a relationship between the administration of blood products and the incidence of multiple organ failure but are unable to distinguish statistically between the possible adverse effects of the blood itself and transfusion as a marker of worse injury [53]. However, misidentification of donors, recipients with acute hemolytic transfusion reactions, administration of bacterially contaminated blood products and TRALI are all associated with transfusion-related deaths each year in the USA and Britain [54].

To reach a homeostasis between dilutional coagulopathy and the risk of rebleeding, the cardiovascular consequences of traumatic anemia and the risk of transfusion-related adverse events remains both difficult and obscure. Currently, the best resort to cope up with this issue is early evaluation and management of the coagulopathy of trauma thereby decreasing the need for massive transfusion and its attendant risks.

CONCLUSION

Fortunately, only a small percentage of trauma patients will require massive transfusion. But, in these patients there is a significant trauma-induced coagulopathy which is aggravated secondarily by dilution and consumption of coagulation factors and platelets, requiring interdisciplinary teamwork.

The implementation of a well-structured worksheet and standard operating procedures with clearly allocated tasks and therapeutic options is necessary to improve the clinical outcomes of patients with life-threatening massive hemorrhage.

These patients should benefit from the optimal management of fluid resuscitation, blood transfusion (early change to a fixed ratio of FFP:PRBCs of 1:1), and the treatment of trauma-induced coagulopathy. The use of recombinant factor VIIa is only justified if replacement therapy of blood components and coagulation factors fails to cease major bleeding.

Only 2% of civilian trauma patients and 8% of military casualties are likely to require massive transfusion and therefore are likely to benefit from greater exposure to plasma and other blood products. Severe injury, shock and evidence of rapid or uncontrollable bleeding are the clinical indicators that suggest the need for the early use of plasma to prevent coagulopathy. After acute resuscitation, conservative blood guidelines should apply. Better tools for hemorrhage control and physiologic assessment are needed.

Whilst massive hemorrhage continues to be a major cause of mortality, it is often reversible, and can be adequately managed by early identification of source of their bleeding, approaching them with consideration of diagnosis, prevention and treatment of the lethal triad and damage control surgery to stop the bleeding.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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