Massive transfusion in multi-trauma patients

Karlijn JP Van Wessem, Bas A Twigt, Kaj ten Duis, Luke PH Leenen

ABSTRACT

Introduction: Trauma is not only the leading cause of death in patients under 45 years of age, but also the most common cause for massive transfusion. Adequate recognition of the need for massive transfusion is paramount to decrease early mortality. Massive transfusion protocols have been developed to simplify and standardize transfusion administration are based on prevention of coagulopathy, acidosis and hypothermia. Transfusion not only refers to administering packed red blood cells (PRBC), but also limiting coagulopathy by means of using essential hemostatic blood products, such as fresh frozen plasma (FFP) and platelets (PLT).

Case Series: In this article, current opinions on massive transfusion will be discussed, based on three patients who received massive transfusion after major injury. All of the three described patients in this article developed coagulopathy, acidosis and hypothermia. Their physiology was corrected by a combination of damage control surgery and early hemostatic blood transfusion. The two surviving patients did not develop any septic complications caused by massive transfusion. At our institution, a 1:1:1 ratio of PRBC:FFP:PLT is advocated, in concordance with most current literature. Massive transfusion, however, can lead to complications such as transfusion induced lung injury, acute respiratory distress syndrome and multiple organ dysfunction syndrome.

Conclusion: In this article, current literature is reviewed, and new insights regarding coagulation measurements and hemostatic products including the influence of transfusion on the immune system have been discussed.

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Keywords: Multi-trauma, Coagulopathy, Acidosis, Hypothermia, Massive transfusion

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INTRODUCTION

Trauma is the worldwide leading cause of death in people under 45 years of age. Yearly, more than five million people die due to trauma related injuries [1, 2]. Trauma is also the most frequent cause of massive blood transfusion. After brain injury (60%), hemorrhagic shock (30–40%) is the most common cause of death in trauma patients [3–5]. Resuscitation strategies during damage control surgery may be as important as anatomical repair in order to improve long-term outcomes [6]. Early recognition of the need for massive transfusion, in combination with aggressive surgical and non-surgical hemorrhage control, results in significant decrease of early mortality. However, massive blood transfusion is associated with high morbidity and mortality rates.

Herein, we will discuss three patients who received massive blood transfusion after sustaining severe

Karlijn JP Van Wessem¹, Bas A Twigt¹, Kaj ten Duis², Luke PH Leenen²

Affiliations: ¹MD, PhD, Department of Trauma Surgery, University Medical Center Utrecht, Utrecht. The Netherlands;

²MD, Department of Trauma Surgery, University Medical Center Utrecht, The Netherlands

Corresponding Author: KJP van Wessem, MD, PhD, Department of Trauma Surgery, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands; Tel: +31 88 75 598 82; Fax: +31 88 75 550 15; E-mail: kwessem@umcutrecht.nl

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traumatic injuries, and describe the effects of receiving massive transfusion. At our institution, we advocate a 1:1:1 ratio of PRBC:FFP:PLT transfusion. Our protocol will be discussed and compared to current literature. Furthermore, recent developments and opinions on blood product ratios, clotting assays and hemostatic products will be reviewed.

CASE SERIES

Case 1: Patient A, a 74-year-old male cyclist, was hit by a car. At the scene, he was intubated because of respiratory distress and two large bore cannulas were inserted. In the emergency department, soft but symmetric breathing sounds were heard and several rib fractures were palpable on the right side. Saturation was 90%, blood pressure 63/27 mmHg and pulse 133/min. The abdomen was not tender and the pelvis was stable. The right tibia had a Gustilo-Anderson grade IIIA open fracture and was actively bleeding; a pressure bandage was applied. The chest X-ray showed a right sided hemothorax and therefore a chest tube was inserted and three litres of bloody fluid was drained. Pelvic X-ray showed an acetabular and subtrochanteric fracture on the right, a bilateral pubic fracture, as well as a suspicion for widened sacroiliac joints. Focussed assessment with sonography for trauma (FAST) was negative. Blood pressure stayed low despite two litres of normal saline and five packed red blood cells (PRBC). The laboratory values at the time of presentation is: hemoglobin (Hb) 4.9 mmol/L, pH 7.00, base excess (BE) -17.2 mEq/L and temperature 35.5°C. The patient was taken to the operating theatre for a right sided thoracotomy. No active bleeding was found from either the lung or the pulmonary vessels. However, a right diaphragmatic rupture was diagnosed. In a subsequent laparotomy, a ruptured bladder along with a retroperitoneal hematoma was found. During the procedure, blood pressure remained low (90/50 mmHg) despite massive transfusion of blood products. After placing a C-clamp to stabilize the pelvis, blood pressure rose to 110/50 mmHg and pulse decreased to 100/min. The chest was primarily closed and the abdomen was temporarily closed by a vacuum pack. Postoperative angiography showed contrast blushes from both internal iliac arteries. Therefore, both internal iliac arteries were coiled. After angiography a computed tomography (CT) scan showed a skull fracture with a subdural hematoma. The patient was then taken to the intensive care unit (ICU), having received 28 units of PRBCs, 21 fresh frozen plasma (FFP), and 30 units of platelets (PLT). After transfusion, Hb was 4.4 mmol/L, pH 7.19, BE -14.6 mEq/L, activated partial thromboplastin time (APTT) >120 sec, prothrombin time (PT) was 26.2 sec, International Normalized Ratio (INR) 1.80, platelets 94x10⁹/L. His temperature was 33.7°C. The patient's neurological condition deteriorated during the following hours in the ICU. A cranial CT scan was repeated and

showed more diffuse cerebral swelling with herniation. Due to a futile prognosis, treatment was withdrawn and the patient died.

Case 2: Patient B, a 49-year-old male cyclist, was hit by a sports utility vehicle. On arrival in the emergency department, he was intubated because of respiratory distress and multiple facial fractures. He had symmetric bilateral breath sounds, but subcutaneous emphysema on the left side. A chest tube was inserted, which drained 300 mL of blood. His blood pressure was 60/40 mmHg and pulse 130/min. His abdomen was distended and the pelvis was stable as were both femurs. His Glasgow Coma Scale (GCS) was 15. Chest X-ray showed a chest tube on the left side in good position, lung contusion and several rib fractures. The FAST showed free fluid. The laboratory values at the time of presentation is: Hb 2.7 mmol/L, BE -11.5 mEq/L, APTT >120 sec, PT 34.6 s, and INR 2.33. Our massive transfusion protocol was initiated and the patient was immediately transported to the operating theatre. During laparotomy a splenic rupture and an avulsed left kidney were found, requiring splenectomy and nephrectomy. The abdomen was packed and a vacuum dressing was applied. After being transported to the ICU, he had received 5.5 liters of Ringer's lactate, 11 units of PRBCs, 6 FFPs and 10 PLT units. Despite massive transfusion, the patient was transported to the theatre twice again during the next few hours due to hemodynamic instability. The second operation showed diffuse oozing from the kidney bed. A few hours later, an ischemic transverse colon was found and resected based on a ruptured middle colic artery. At that time, he had received 51 PRBC units, 50 FFPs, 45 PLTs. The hemoglobin then was 6.0 mmol/L, pH 7.37, BE -2.8 mEq/L, platelets 58x10⁹/L, APTT 38 s, PT 10 s, and his temperature was 35.9°C. After stabilization, a CT scan was performed a few hours later which showed a subdural hematoma on the right frontotemporal side, a Le Fort I facial fracture, C6 facet joint fracture, transverse process fractures of L2-L4, and several rib fractures on the left side. On the third day his colon was anastomosed, on eight day the abdomen was closed, and on day ten and fifteen his facial fractures were repaired. Apart from a bleeding peptic ulcer postoperatively, no further complications occurred, and six weeks after arrival, he was discharged to a rehabilitation center.

Case 3: Patient C, a 48-year-old male driver hit a tree. Upon arrival in the emergency department his airway was threatened because of blood in his mouth. There were bilateral soft but symmetric breathing sounds and the left side of his chest was painful on palpation. Saturation was 75%, blood pressure 125/75 mmHg, pulse 125/min, and GCS 11 (E3M6V2). A chest X-ray showed multiple fractured ribs on the left side, but no pneumothorax. A pelvic X-ray showed no abnormalities. His abdomen was not tender, but a FAST of the abdomen showed free fluid. The patient was intubated and a left chest tube was inserted. Additional X-rays revealed a comminuted femur and patella fracture on the left side.

The first measured Hb was 8.4 mmol/L, pH 7.40, BE -7.0 mEq/L, platelets 154×10^9 /L, PT 15 s and APTT 32 s, and INR 1.10. The patient was prepared for CT scan, but because of hemodynamic instability despite resuscitation he was transported to theatre for a laparotomy. A caval vein injury was diagnosed with a partially avulsed left kidney, a contused transverse colon with several serosal tears and a vascular pancreatic injury. The caval vein injury was sutured, a left nephrectomy was performed, the transverse colon resected and the abdomen was packed and a vacuum pack was applied. The femur was stabilized with an external fixator. By then the patient received 18 PRBC units, 18 FFPs and 20 PLTs. The hemoglobin was 4.5 mmol/L, pH 7.10, BE -9.7 mEq/L, platelets 116×10^9 /L, PT 16.6 s, APTT 42 s, and INR 1.20. After 24 hours, a second look laparotomy was performed whereby the colon was anastomosed and the abdomen closed. On third day, the patient developed respiratory distress despite being on a ventilator with high pressures and high FiO₂ values. Therefore, the femur was left with the external fixator and no intramedullary nailing was performed. The CT angiography of the chest revealed no abnormalities [no signs of pulmonary emboli, Adult Respiratory Distress Syndrome (ARDS) or pneumonia]. A few days later, he developed fever and a relaparotomy was done and large amounts of pancreatic necrosis were found and resected. The colon anastomosis was intact. On day 21, he developed chylous leakage and was put on total parenteral feeds. Chylous leakage ceased and oral feeding could be resumed after a few weeks. Four weeks after the accident the patellar fracture was fixed, and three weeks later, the patient was discharged to a rehabilitation center.

DISCUSSION

Lethal triad of hypothermia, acidosis and coagulopathy

The three described cases show severely injured patients with persisting hemodynamic instability based on hypovolemic shock. Shock causes a shift from aerobic to anaerobic metabolism resulting in acidosis. Furthermore, patients in shock develop hypothermia; they do not only lose warmth during the trauma itself, initial assessment and operations, but also because of massive transfusion of blood products. Hypothermia causes arrhythmias, decreased heart minute volume, increased vascular resistance and a shift to the left in the oxygen-hemoglobin saturation curve. Thirdly, these severely injured patients develop coagulopathy. Previously, it was assumed that dilution by resuscitation was the most important factor causing coagulopathy. Current insights, however, show that coagulation cascade and platelets are not only influenced by hemodilution but also by acidosis and hypothermia. A temperature of 32°C equates to clotting factor activity of 2.5% of normal. It is postulated that

the major effect on clotting factors during hypothermia is on the kinetic activity of clotting enzymes. Therefore, the appropriate treatment for hypothermia induced coagulopathy is rewarming rather than administration of clotting factors [6]. Coagulopathy develops in the early phase after injury and is not related to fluid resuscitation. Coagulopathy is a marker for injury severity and is related to mortality [7]. Moreover, hypovolemic shock and transfusion itself induce fibrinolytic system consumption by activating the coagulation cascade [7]. In international literature the combination of hypovolemia, hypothermia and acidosis is called the 'lethal triad'. The treatment of patients is focussed on preventing this dangerous vicious cycle.

Massive transfusion of blood products

The presented patients all received massive transfusion of blood products after sustaining severe injuries [8]. The definition of massive transfusion is administration of more than ten PRBCs in 24 hours, more than one entire blood volume in 24 hours, more than four PRBCs in one hour, or more than 50% of total blood volume within the first three hours [9, 10]. Massive transfusion is associated with increased mortality: more than six PRBCs within 24 hours have a mortality of 20–30%, more than 10 PRBCs within 24 hours are associated with mortality as high as 50% [11]. Length of stay in ICU is longer if patients receive more than six PRBCs (more than ten days versus four days if the patient received less than four PRBCs). If transfusion exceeds six PRBCs the total hospital stay is also longer. Blood product transfusion can cause adverse effects such as transfusion reactions, infection transmission and has an immune modulatory response. After blood product transfusions, an increase is seen in wound infections, pneumonias, sepsis, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), transfusion related acute lung injury (TRALI) and multiple organ dysfunction syndrome (MODS) [12, 13].

For a long time, it has been unclear what transfusion protocol was associated with lower morbidity and mortality. In the military, it has already been long advocated to use massive transfusion protocols in which the administration of blood product combinations resembled whole blood [14, 15]. It is clear now that in the civilian population the administration of a higher FFP:PLT:PRBC ratio is also associated with lower mortality [5]. It became also clear that a good-working massive transfusion protocol is paramount for optimal results. Cotton et al. demonstrated that administration of blood products according to a predefined protocol in the early phase of resuscitation leads to less MODS, less infectious complications, decrease in ventilation days and reduction of abdominal compartment syndrome and incidence of open abdomens [16].

Several studies have shown that early correction of coagulopathy is associated with increased survival [5,

8, 9, 14–19]. In other words, massive transfusion based on a more physiologic regime resembling whole blood will improve survival. With reference to good results in several studies a new international consensus has been developed: A ratio of 1:1:1 in PRBC:FFP:PLT is advocated [9, 20–22]. This ratio results in decreased mortality, less blood products needed and decreased costs per patient. In our hospital, we also strive towards a 1:1:1 ratio. The pillars of our protocol are: stop the bleeding, be flexible regarding hypotension, perform damage control surgery when needed, minimizing the use of crystalloid fluids, start early with blood products (aiming at a ratio of 1:1:1), administer tranexamic acid and use thromboelastography in multiple transfusion patients (>5 PRBC).

In literature, it is mentioned that it might be difficult to reach a 1:1:1 ratio in practice because O negative PRBCs are readily available in the emergency department, while FFPs and PLTs usually need to be prepared. The transfusion ratios, obtained in patients A, B, and C were 1.3:1:1.4, 1.1:1.1:1, and 1:1:1.1, respectively. To reach these ratios it is paramount to optimize the cooperation between the blood bank and the anesthesiologist who coordinates blood product administration.

It is important to note that the transfusion consensus is mostly based on retrospective studies since it is very difficult to randomize severely injured patients for a specific transfusion ratio. Furthermore, there is evidence that this management may cause more complications such as SIRS, TRALI and MODS [12]. Possibly, this is caused by increased FFP and PLT administration. Due to this, some authors are warning against the development of protocols for empirical FFP transfusion [23]. Other authors stress the importance to administer FFP when it is physiologically necessary and not simply when there is laboratory evidence of coagulopathy [24]. This pleads for a more individual approach, adjusting the transfusion ratio on the basis of post-injury changes in the clotting and fibrinolysis cascade. In a recent review Sorensen et al. speculate that timely and rational use of systemic antifibrinolytics, local hemostatics and coagulation factor concentrates (fibrinogen, prothrombin complex concentrate, recombinant factor VIIa and factor XIII) will be more efficacious and safer than ratio-driven transfusions [25]. Innerhofer et al. have recently shown in a prospective cohort study that prothrombin complex concentrates (PCC) are effective in correcting coagulopathy and reducing the need for transfusion in patients with severe blunt trauma [26]. However, larger randomized trials need to be conducted to evaluate this effect since an increased risk of thromboembolic events has been reported in the past as well [27]. We believe until that time has come, it is safer and more useful to have an uniform protocol.

In the cases described above, none of the two surviving patients developed TRALI, ARDS or MODS despite massive transfusion administration. It could be noted that massive transfusion may have attributed to brain swelling causing patient A to develop cerebral

herniation. However, it will remain unclear whether cerebral herniation would have been prevented if he had not received massive transfusion.

Thromboelastography

In massive transfusion patients APTT and PT have shown to be bad predictors for coagulopathy and the need for transfusion [28]. New insights regarding clotting measurements have led to the introduction of the thrombelastograph hemostasis analyzer (TEG). Thrombelastography has proven, in contrast to APTT and PT, to be a simple viscoelastic test of overall coagulation by measuring clot strength, which reflects the quantity and quality of both clotting factors and platelet function. Furthermore, it is a rapid (several minutes versus 45 minutes for APTT and PT) and inexpensive test. Treatment of coagulopathy can be focussed on the consumed clotting factors because TEG determines coagulation directly [4, 29]. The TEG has recently been implemented in our hospital and some studies indicate that transfusion ratios might be further adjusted even more, based on TEG measurements. Eventually, it might lead to transfusion ratios personalized to the specific patient's needs [24].

Blood product replacing therapies

In recent years, blood product replacing therapies have gained more and more interest. Several products are described below.

Recombinant activated factor VII (rFVIIa) has been used for some time for spontaneous bleeding in hemophilic patients. It enhances clot formation in combination with tissue factors expressed on damaged or ischemic vascular subendothelium. It binds directly to activated platelets, thereby stimulating a stable hemostatic plug formation. rFVIIa, however, is very expensive. Recently, a large multicentre trial studying rFVIIa in multi trauma patients has been terminated because no increased survival could be demonstrated, even though the number of blood products in rFVIIa-treated patients decreased [2].

Part of the response to trauma and surgery is fibrinolysis. This response can be so large that it becomes pathological due to hyperfibrinolysis. Antifibrinolytics decrease blood loss in patients with both normal and pathological responses without apparent increases in postoperative complications [30]. Tranexamic acid is a synthetic derivative of amino acid lysine that inhibits fibrinolysis by blocking lysine binding sites on plasminogen and in contrast to rFVIIa, the treatment is inexpensive. Several clinical studies have researched tranexamic acid in trauma patients. The Lancet has published a randomized clinical trial including more than 20,000 patients showing a significant decrease in mortality in multi trauma patients treated with tranexamic acid. Furthermore, mortality caused by bleeding was significantly lower when treated with tranexamic acid [31].

Fibrinogen plays an important part in hemostasis through its role in platelet aggregation formation and construction of a stable fibrin network. Current transfusion strategies are based on reaching adequate coagulation by administration of FFPs and PLTs. Cryoprecipitate (a combination of Factor VIII, fibrinogen, fibronectin, von Willebrand factor and Factor XIII) is mainly used when fibrinogen blood levels are too low. Fibrinogen concentrations in cryoprecipitate are much higher than in FFP. When cryoprecipitate is administered to correct fibrinogen levels, the volume added is much lower than when FFP is used. This is favorable in reducing complications related to massive fluid resuscitation. At this moment, it remains unclear whether normal fibrinogen levels in trauma patients are recommendable [32].

Hemoglobin based oxygen carriers (HBOC, hem-tetrameres) are human blood derivatives and developed in the United States for military purposes. Studies have demonstrated that HBOCs have a number of advantages, namely being always compatible, they do not transmit diseases, have no immunological side effects, and can be stored long-term [33]. In 2008, Moore et al. published a multicenter randomized double blind trial comparing HBOC administration in a pre-hospital setting with customary administration of crystalloids and PRBCs. No statistical significant difference could be demonstrated in a 30-day mortality between both groups. However, there were more complications reported in the HBOC treated group. Consequently, it was advised to consider HBOC treatment only if blood products are not available, such as in war or disaster situations [33].

Inflammatory response induced by massive resuscitation

Although blood transfusions are lifesaving, some studies suggest that patients receiving blood transfusions with older PRBCs have worse clinical outcomes including sepsis and MODS than patients who receive fresh blood [34, 35]. With increased storage time, PRBCs change in biochemical composition and morphology resulting in erythrocyte lysis. Neal et al. have shown that transfusion of intra-erythrocytic compounds may have adverse reactions, especially with long stored PRBC units or in massive transfusion. Free heme released from hemolysis exerts an impact on multiple components of the innate immune response, both through effects on NO depletion as well as cellular specific mechanisms [36].

Microparticles (MP) are vesicles that are thought to bud from apoptotic or activated cells and retain the surface markers of their parent cell [37]. It is likely that erythrocytes undergo MP formation as they age. These MPs appear to contribute to neutrophil priming and activation. The presence of MPs in stored units can be associated with adverse effects after transfusion, including lung injury [38].

During the last years the efficacy of various blood products used as resuscitation fluid on the acute

inflammatory response after hemorrhagic shock has been investigated. Makely et al. have shown that resuscitation with fresh whole blood ameliorated the inflammatory response after hemorrhagic shock and that crystalloids in mice induced a larger inflammatory response compared with fresh whole blood [39]. Subsequently, they investigated the use of different ratios of PRBCs and plasma and found that a 1:1 ratio of PRBC to plasma is nearly as efficacious as fresh whole blood [40]. Further, removing MPs from aged blood before use proved to be beneficial because of the reduction in inflammatory response [40].

Not much is known about the influence of fresh frozen plasma administration on the immune system. The FFP contains leukocyte-derived bioactive substances that can sometimes cause transfusion related lung injury (TRALI) and/or anaphylactic shock [41]. These adverse reactions are thought to be an expression of a pro-inflammatory response. This was confirmed by in vitro studies by Urner et al. [42]. They found that blood products are able to provoke a pro-inflammatory response in endothelial cells, especially when cells are already pre-activated. Nohe et al. have investigated the role of FFP on the endothelial cell adhesion molecules and subsequent neutrophil-endothelial interactions in vitro. They found that FFP reduced the adhesion molecule expression and subsequent adhesion of neutrophils on the endothelium. This suggested that FFP also have an anti-inflammatory effect [43]. This can possibly be attributed to fibrinogen. Several studies have shown that fibrinogen induces a pro-inflammatory response by interaction with neutrophil MAC-1 (complement receptor consisting of CD11b/CD18) facilitating neutrophil adhesion to the endothelial wall [44, 45]. In vitro studies from our own research group however have shown that fibrinogen has an anti-adhesive role in regulating neutrophil-endothelial interactions [46]. Cryoprecipitate contains higher concentrations of fibrinogen than FFP. Interestingly, a retrospective study analyzing polytrauma patients showed less organ failure when cryoprecipitate was administered instead of FFP [47]. One could speculate that the anti-inflammatory effect of fibrinogen has attributed to these results.

To date, the exact role of blood products in the inflammatory response remains unclear.

CONCLUSION

This case report shows that multi trauma patients in hypovolemic shock do not only benefit from damage control surgery but also from adequate transfusion management. It is paramount to prevent the 'lethal triad'. Transfusion management is not only focussed on packed red blood cells administration, but also on supplying necessary clotting factors to limit coagulopathy. We not only advocate a 1:1:1 transfusion ratio from a hemostatic point of view, but it has also a less detrimental effect on the inflammatory response. In two out of our three

patients a 1:1:1 transfusion ratio was feasible. Patient A had a 1.3:1:1.4 ratio. This was mainly due to lack of initial available fresh frozen plasma (FFP) in the emergency department. To solve this problem, it could be advocated to have FFPs readily available in emergency department at all times. In the near future, coagulation will be measured more quickly and more accurately by thromboelastograph hemostasis analyser. It is expected that this technique will soon be available in emergency department, ICU and operating theatres. This development will increase adequate coagulopathy correction. At the moment, tranexamic acid is the most promising blood replacing product.

Author Contributions

Karlijn JP Van Wessem – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Bas A Twigt – Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Kaj ten Duis – Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Luke PH Leenen – Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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