Massive Transfusion Practices Around the Globe and a Suggestion for a Common Massive Transfusion Protocol

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Background: Massive transfusion, the administration of 10 to more than 100 units of red blood cells (RBC) in less than 24 hours, can be a life-saving therapy in the treatment of severe injury. The rapid administration of large numbers of RBC, along with sufficient plasma and platelets to treat or prevent coagulopathy, is frequently a disorderly process. Patient care and collaborative research might be aided with a common protocol.

Methods: The authors polled trauma organizations and trauma centers to find examples of massive transfusion protocols. The goals and ease of use of these protocols were evaluated.

Results: Massive transfusion protocols exist at a relatively small number of large and well-organized trauma centers. Most of these protocols are designed to treat pre-existing and/or ongoing coagulopathy.

Conclusions: The evidence would suggest that prevention of coagulopathy is superior to its treatment. Simple ratios such as 1:1:1 RBC:plasma:platelets have the benefit of ease of use and the relatively higher plasma and platelet doses appear to be associated with improved outcome. Such a standard protocol can foster multicenter research on resuscitation and hemorrhage control. The fixed volume ratios might allow the number and rate of administered units of RBC to be used as surrogates for blood loss and primary treatment effect.

Key Words: Blood transfusion, Massive, Trauma, Protocol, Resuscitation, Outcome.

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METHODOLOGIES

Massive transfusion protocols were sought in the medical literature. Trauma care organizations, trauma centers, specific experts in trauma, and all of the members of this symposium were contacted by phone or e-mail and asked to submit massive transfusion protocols used by their organizations.

Protocols obtained were evaluated for their goals, structure, and the likelihood of achieving their objectives. Goals, stated or implied, were to correct or prevent the coagulopathy associated with trauma resuscitation. The likelihood of achieving these goals was most often addressed in terms of the numbers of units of plasma and platelets administered, expressed as a ratio to the number of units of RBC transfused. The authors admit a preference for prevention, higher ratios, and simplicity of bedside management.

FINDINGS

Despite an extensive search, the authors found relatively few institutions with massive transfusion protocols. Moreover, the protocols shared with us were often designed to treat dilutional coagulopathy or to demonstrate that a sufficient attempt had been made at treatment to justify the use of recombinant factor VIIa (rFVIIa). What is available fell into three general categories: organizational guidelines, protocols in use outside of the US and protocols in use at US institutions.

ORGANIZATIONAL GUIDELINES

Guidelines developed by the American Society of Anesthesiologists (ASA) for administration of blood components in surgery state that in general, the goal of replacement therapy is a platelet count of >50,000/mL, reduction of prothrombin time (PT) to 15 seconds and of activated partial thromboplastin time (PTT) to 40 seconds. This is with the assumption that control of bleeding is imminent. Cryoprecipitate may be included to support fibrinogen, vonWillebrand factor (vWF), and factors VIII and XIII. Physicians from the British National Blood Service, Northern Zone have integrated these guidelines into their trauma transfusion guidelines. Other organizational guidelines are described below as they are directly incorporated into some existing massive blood transfusion protocols.

MASSIVE TRANSFUSION PROTOCOLS OUTSIDE OF THE UNITED STATES

The transfusion protocol developed for use at the University of New South Wales, Sydney, Australia, is based upon a “rescue” model. This protocol specifies that resuscitation continue until the source of bleeding is controlled, and blood products are given when clinicians perceive that these products are needed. This protocol addresses the identification and management of both surgical and medical causes of bleeding, to include surgical control of bleeding sites and prevention or reversal of hypothermia, acidosis, coagulopathy, anti-coagulation (e.g. due to warfarin) and consideration of anti-fibrinolytic agents. This protocol stipulates transfusion of 1) 4 units of fresh frozen plasma (FFP) if the PT or PTT is greater than 1.5 times normal, 2) 10 units of cryoprecipitate if the fibrinogen level is <1 g/L, 3) 4 units of platelets if the platelet count is less than 75 × 10^9/L. If bleeding and coagulopathy continue after conventional therapy (defined as 10 units of RBC, 8 units of FFP, 8 units of platelets, and 10 units of cryoprecipitate) then rFVIIa is given at a dose of 100 µg/kg.

The massive transfusion protocol of the Centre Hospitalier Intercommunal in Poissy, France, incorporates treatment intended to prevent coagulopathy and acidosis and includes specific guidelines regarding blood product transfusion. This protocol specifies that 8 units of RBC be issued initially, usually group O Rh negative or type-compatible without further testing unless the patient has known antibodies. Serial laboratory testing is performed. Thawed FFP is issued in ratios of 4 FFP/6–8 RBC. Platelets are given at a dose of one unit per 7 kg with a goal of achieving platelet “counts” of 50–70 × 10^9/L. With evident bleeding, the FFP/RBC ratio is increased to 6–8 units/8 units of RBC, and cryoprecipitate and rFVIIa (60–90 µg/kg) are considered as well.

A similar protocol was designed by the Massive Transfusion Task Group at the Helsinki University Hospital in Finland. Minor differences include the initial and subsequent issue of 10 units of RBC at a time and the issue of RBC to maintain a goal hemoglobin concentration of 10 g/dL and platelets at a concentration of >50 × 10^9/L.

MASSIVE TRANSFUSION PROTOCOLS IN USA TRAUMA CENTERS

In the US, there are no medical institutional requirements for massive transfusion protocols. The American College of Surgeons’ Committee on Trauma (ACS-COT), as part of the trauma center certification process, inquires whether the applicant institution has such a protocol, but existence of a massive transfusion protocol is not a requirement for certification. Those protocols that do exist appear to have three main components: early transfusion requirements while gaining control of bleeding, anticipation of further transfusion needs, and the role of laboratory support.

The Denver General Health Center protocol follows this basic outline. Upon presentation of a patient deemed likely to need massive transfusion, a blood sample is sent to the laboratory for type and cross-match of 10 units of RBCs (a common procedure in many institutions). After the first 6 units have been transfused, the blood bank is warned of the potential need for additional units and the order is given to begin thawing 2 units of FFP, if this has not already been started. If additional RBCs are requested, a “Request for Emergency Release” form is completed, and the Massive Transfusion Protocol is activated. When additional RBC are requested at a rate of 4 units per hour or more, official activation of the protocol allows type-specific or ABO compatible RBC to be released without cross-matching. No cross-
matching is required within a 24-hour period once the patient has received more than one blood volume. Transfusion of FFP and platelets start when non-surgical bleeding, “oozing”, appears or when coagulation laboratory results are abnormal. Laboratory values thenceforth guide further transfusion of RBC, FFP, and platelets.

The University of Texas, Houston (UTH), has also developed and implemented a massive transfusion protocol. Shortly after a patient with severe, difficult-to-control bleeding is admitted to the emergency department (ED), the trauma surgeon orders transfusion of O-negative RBC (4 units stored in the ED) and invokes the massive transfusion protocol by calling the blood bank to explain the situation. A runner is sent to the blood bank with a blood sample and returns with an insulated container that contains 6 units of RBC (O-negative if time does not permit typing of the blood sample) and 4 units of newly-thawed FFP. Subsequent containers, with 6 units each of RBC and thawed plasma, are sent as requested for ongoing hemorrhage. One “dose” (6 units of whole-blood-derived random donor or 1 apheresis unit from a single donor) of platelets is also sent; this dose is repeated after every additional 12 units of RBC. Goals are to normalize the PT and to raise the platelet count to 100 × 10⁹/L. After 18 units RBC, the fibrinogen level is checked and if the fibrinogen level is less than 1 g/L, 10 units of cryoprecipitate are given. This protocol remains active until the patient arrives in the ICU, after which further therapy is based upon specific laboratory abnormalities.

The protocol of the University of Maryland R Adams Cowley Shock Trauma Center (STC) in Baltimore is designed to minimize the coagulopathy of trauma. Red blood cells, plasma, and platelets are used early in the resuscitation of massively bleeding patients, soon after patient arrival at the trauma resuscitation unit (TRU). Infusion of crystalloid has often been started in the field and continues in the TRU with Plasmalyte-A, an isotonic crystalloid similar to Ringer’s solution. Blood is sent immediately to the blood bank for typing and cross-matching. Twelve units of un-cross-matched group O RBC are kept in the TRU blood refrigerator and are available for immediate use. Two of the units are O Rh Neg, and are usually reserved for women of child-bearing age. This un-cross-matched blood is used for immediately life-threatening hemorrhage until type-compatible or fully cross-matched blood is available. Type-compatible RBC and plasma are generally available within 30–45 minutes.

During ongoing massive transfusion, blood is typically ordered in amounts of 10 units of RBC, 10 units of plasma, and an apheresis platelet pack equivalent to 6–11 units. Because RBC are issued on the basis of a computer cross-match (are type-compatible) and type compatible thawed plasma is maintained in the blood bank, the delay between order and issue is minimal once a blood type has been established. Resuscitation managers, usually anesthesiologists, give the RBC and plasma alternately and the platelets at the end of a 10 RBC unit course. This protocol supports a definite order of resuscitation, that is, crystalloid, RBC, plasma, and platelets. By the time that 20 units of RBC are given, essentially all patients with ongoing massive transfusion are receiving the blood components in a 1:1:1 ratio. (Cryoprecipitate is rarely given at the STC. In calendar year 2000, only 4 patients were treated and 64 units administered.)

**Discussion and Proposed Protocol**

Dilutional coagulopathy is well-described in the medical literature. Hirshberg and his colleagues have used mathematical modeling to show that initial resuscitation with more than five units of RBC in additive solution inevitably leads to dilutional coagulopathy, and Armand and Hess note that ongoing resuscitation with RBC, plasma and platelets in a 1:1:1 ratio can barely keep up with ongoing dilution as a “best-case scenario.” Discussants at this symposium concurred that the most severely injured patients, destined for massive transfusion, typically receive large amounts of crystalloid, followed by un-cross-matched RBC as soon as the units are available. Such therapy continues for at least 30–45 minutes because that is the length of time required to type blood and then prepare and issue type-compatible plasma and platelets. Thus, by the time that plasma and platelets are available, the plasma of the most severely injured and rapidly hemorrhaging patients will have already been diluted sufficiently to meet conventional criteria for plasma therapy. If treatment continues for another 10 units of RBC and 10 units of plasma, the platelet count can be expected to be in the range of 50–100 × 10⁹/L purely on the basis of dilution and even lower if significant consumption is occurring. Thus, even in the absence of immediately available laboratory confirmation, platelet support is appropriate at that time in the face of massive ongoing bleeding.

Based upon the review of the literature, evaluation of available protocols and symposium discussion, we propose the following massive transfusion protocol. It recognizes that the initial treatment of the most severely injured patient is chaotic and resource-limited. Such patients will likely receive crystalloid fluids and un-cross-matched RBC before the full extent of their injury is known. However, once the clinical situation clarifies sufficiently that a massive transfusion protocol is called for, such protocols must provide 1) as much plasma support as can be given without compromising the delivery of RBC and 2) enough platelets to keep the platelet count well above 50 × 10⁹/L. Our proposed protocol utilizes a 1:1:1 ratio, that is, 1 unit RBC to 1 unit FFP to 1 conventional (not apheresis) unit of platelets. Where apheresis units of platelets are used, these are equivalent to 6–11 units of conventional platelets. Therefore, to simplify administration at the bedside, RBC and plasma units are given alternately until 10 units of each are infused, followed by a unit of apheresis platelets.

One must recall that protocols such as this are not invoked until treatment is well underway. The most severely injured patients will receive 2 to 10 units of un-cross-matched
RBC in the time taken to activate the protocol and another 10 units of protocol RBC with 10 units of plasma and 6 to 11 units of platelets before the effect of their treatment is approximately uniform. Thus, relative uniformity of care can only be realized in those who ultimately require more than about 20 units of RBC during primary resuscitation. Como and his colleagues, in their review of blood use at the Baltimore center, found that only 68 of 5643, that is, 1.2%, of patients directly admitted from the scene of injury received more than 20 units of blood.12

The participants in this symposium also emphasized that once bleeding is controlled and the patient is hemodynamically stable, the issues change to maintaining hematologic function. Clinicians are now able to incorporate beside and laboratory measures as transfusion guides. Conventionally, follow-up laboratory assessment is done every 6 hours for the first 12 hours post-stabilization and then at 24-hours post-stabilization. If there is no evidence of active bleeding, abnormal PT, PTT, and platelet counts should not be treated with transfusion. If there is concern for continuing low-level bleeding (ooze), FFP is transfused if the PT is 1.5 times normal. Platelets are given if the platelet count is less than 50 x 10⁹/L. RBC will be transfused for hemoglobin less than 100 g per liter for the first 24 hours of maintenance. This allows a safety margin for the rebleeding and dynamic fluid shifts that are inevitable after resuscitation. After the first 24 hours, a restrictive transfusion trigger (maintenance of Hb at 70–90 g/L) and the patient’s clinical condition should guide further RBC transfusion.

The massively transfused patients described by Como and his colleagues had a 50% mortality rate and used 50% of all of the blood products used in the center. This implies that therapies that impact mortality and blood product usage should be easy to identify. Moreover, patients who received 20 units of RBC had equivalent injury severity scores whether they lived or died, suggesting that hemorrhage control determined survival, an observation consistent with the experience of the clinicians at this symposium. To the extent that an intact coagulation system contributes to hemorrhage control, protocols that minimize coagulopathy should reduce blood use and improve survival.20

The fixed blood-component volume ratios given during active hemorrhage in the proposed protocol may allow the number of RBC units administered to be used as a surrogate for blood loss and primary treatment effect. The relationship between blood loss and blood volume administered will be most direct when the number of units of RBC given is large and a protocol that accounts for most of the administered volume has been in effect for some time.

The protocol outlined above must be fully developed and examined in a clinical trial. In the meantime, it serves as a conceptual tool to help surgeons and anesthesiologists define actions from the early chaotic phase of resuscitation to standardized blood product support. It should also encourage blood banks to remove impediments to rapid blood product delivery.21 The feasibility of the protocol and the consequences of its use should be discussed more widely in the medical/surgical community.

REFERENCES

DISCUSSION

Dr. Myung Park: I would like to thank COL Holcomb and Dr. Hess for inviting me to discuss this interesting paper by Drs. Malone, Hess and Fingerhut. The massive transfusion of blood products in the acute trauma can be lifesaving. Vaslef et al. have shown in a retrospective review that aggressive transfusion therapy in the first 24 hours after trauma is warranted and resulted in 43% survival rate in those transfused >50 units of blood products. Also, as shown by Velmahos et al. in their review of 141 trauma patients requiring massive transfusions, the number of blood unit transfusion did not differ between survivors and non-survivors. Hence, aggressive blood transfusion of the exsanguinating trauma patient should not be limited by the need for massive transfusion.

Fortunately, only a small proportion of trauma patients need massive transfusion. But as every surgeon who has encountered a bleeding patient realizes, a ready accessibility of blood products becomes crucial for the survival of that patient. A massive transfusion policy developed in coordination with the blood bank allows a surgeon to get access to the blood products quickly before typed and cross-matched blood becomes available. The authors of this manuscript address the common practices of massive transfusion of trauma patients within the U.S. as well as in other countries. Furthermore, the authors describe an evidence-based massive transfusion guideline for the “immediate resuscitation” period after injury and during the “maintenance mode” when the bleeding is controlled. The recommended ratios of blood products to be transfused published are guidelines and need to be tailored on an individual patient basis as the resuscitation progresses.

Some of the common issues concerning how much, and what products to transfuse during massive hemorrhage, were discussed previously. One of the difficulties of finding a threshold transfusion hemoglobin value is the fact that by the time CBC results are available, as much as 60 minutes have passed and its value may no longer reflect the bleeding patient’s true hemoglobin. So what should the hemoglobin threshold be? Only a randomized, multi-center trial will provide enough power to answer this question. This is easier said than done. And as Dr. Owings pointed out yesterday, the hemoglobin concentration in packed red blood cells is not standardized so that 1 unit of blood is not the same as another. Also, total volume of red blood cells can vary from 50 to 100 cc/unit.

The commonly used plasma clot based assays such as PT and PTT are at best moderately sensitive to reductions in the concentration of coagulation factors. As Dr. Hiippala pointed out yesterday, by the time PT and PTT values increase, plasma is depleted or diluted of 50% of its coagulation factors. The authors have recommended in their manuscript, monitoring PT, PTT, platelet counts every 6 hours for the first 12 hours after stabilization of the patients and then at the 24 hour post-stabilization period. What about during the “immediate resuscitation” phase?

I would also like to ask the authors about the possibility of integrating TEG to guide the type of blood products to be given. This is not to say that during the massive transfusion, a surgeon should be waiting patiently for the TEG result to come back, but rather look at the TEG results to guide more of what type of blood products need to be given.

Unlike the standard PT and PTT, TEG performed at patient’s body temperature, is a whole blood clotting assay, which is more representative of in vivo clotting than a plasma based assay such as the PT and PTT. Information from TEG can be obtained as early as 30 minutes and guide the clinician to the need for transfusion of coagulation factors (FFP) vs platelets or fibrinogen (cryoprecipitate). Again, I advocate that it can be used as an adjunct to surgeon’s clinical impression of what the patient needs during massive transfusion. I think there needs to be a paradigm shift from quantity to the quality of clotting factors at play, as Dr. Delgado mentioned yesterday.

Lastly, I would like to ask the authors and the audience concerning the correction of acidosis (for example, bicarbonate transfusion) as an adjunct to warming and resuscitating the bleeding patient? Martini et al. from our Institute has shown clearly in the porcine model, that pH < 7.1 significantly impaired thrombin generation and had an additive effect with hypothermia <32 C. Meng et al. also showed in his in vitro study that pH, especially less than 7.0 leads to a significant reduction in thrombin generation. Dr. Lefering, in his review of the German Trauma Registry, has shown us that acidosis is an independent predictor of poor outcome. Should we proactively correct acidosis in an actively bleeding patient undergoing massive transfusion, especially when administration of the recombinant factor VIIa is considered?

Dr. Debra Malone: Dr. Park, yes, I think acidosis needs to be addressed. I wouldn’t necessarily give bicarbonate in the immediate resuscitation phase; rather, I’d address the problem of hypoperfusion. The acidosis is in part due to anaerobic respiration in this scenario. I would emphasize volume resuscitation. There is data to suggest that giving bicarbonate in this setting might make the clinical situation worse. TEG, sure, but again, when the result comes back, you have to go back in your mind to where the patient was clinically at that particular time. So you may end up with the same problem. Dr. Hiippala, thank you for your protocol. I agree that the trauma resuscitation doesn’t end when you get control. The trauma team needs to be watching the patient very closely in the post-resuscitative phase, and monitoring needs to continue while the patient is in the ICU. When do you stop? It would be based primarily upon how the patient was doing clinically.

Dr. Seppo Hiippala: I think the authors have done a wonderful job. The item I especially like is the post-transfusion
care. Most guidelines don’t take into account the post-operative phase or the post-transfusion phase, which is quite important. If you think about the patient going to the ICU, that’s where we can ruin all the things we have done the previous 12, 18 hours treating the patient, because at that time, there are many factors causing changes in blood volume. The body temperature rises, there may be changes in vascular resistance and filling pressures, so the patient may need repeated fill-ups. We try to maintain adequate circulatory blood volume, and consequently we may dilute the patient and provoke a new bleeding episode. So we have to monitor the patient very closely to avoid these developments in the post-transfusion phase.

Dr. Mo Blajchman: One point about the group specific. If you use O negative or O positive blood and then you go to group specific, you will need to do a cross-match for subsequent ABC transfusions. So once you give O negative blood, you may need to stay with this type of blood for this patient.

Dr. John Hess: We use computer cross-matching on the initial specimen so we don’t see a passively transferred antibody.

Dr. Hiippala: As the total amount of transfused red blood cells reaches the limit, which is ten units, you start thinking about platelet transfusion. That’s the second side arm of this protocol. And then when you get along with the transfusion and the number of red blood cells increases and you get to the phase when you are suspecting that you have low levels of fibrinogen, you measure it or do not measure it, but may use cryoprecipitate to boost up fibrinogen levels and the von Willebrand factor and so forth. This is the active phase of the protocol, and your goal is to get to the maintenance or stability phase of it.

The 24-hours follow-up which the authors have suggested is a good one. You have to do repeated patient assessment in the ICU and have the laboratory tests on those time schedules and maintain hemoglobin at the appropriate level. If you get abnormal PT, PTT, but the patient is not bleeding, you don’t need anything. But if the bleeding or oozing is going on, you react and give fresh frozen plasma. The same thing applies for the platelets. The question is, as we have these protocols and we are dealing with trauma patients, should we also add in some guidelines when to resort to damage control? I mean, incorporate these protocols with surgical interventions, when to resort to damage control surgery, when to use radiological interventions, and so forth. Every institution should have in-house rules for those procedures.

Then there is another thing which we stressed today very much. There is no use to have any of these protocols if you are unable to deliver the blood products. That’s the number one question. Presently we have a standard procedure that every patient prone to bleed massively will have excellent venous access for massive rapid transfusion with a fluid warmer. These devices have changed the whole scope of our massive transfusions. I stress to my residents that this setup has to be done as early as possible to get hold of the situation. Otherwise you can’t master the situation. Of course, it changes all the time. In this hypothetical setting the blood loss becomes delivery dependent, analogous to the septic patient’s oxygen delivery dependence. We need the massive transfusion capability. And I think the association of poor outcome with acidosis, hypothermia and coagulation, is actually insufficient volume resuscitation. I think all massive transfusion protocols should also have these in-house standard operational procedures. But I think the authors have done a fine job. And I think this protocol incorporates all the important features of other protocols which have been shown here. And I believe it’s something we could do and use clinically also.

Dr. Kurt Grathwohl: I think these transfusion protocols are excellent in that they get the products straight to the patient and they get it to them quickly. The crux of the matter, though, is how much do you give and when do you stop? Dr. Owings’ point yesterday was, there is no substitute for a good clinician, and I absolutely agree. The problem that we have is that we either overtransfuse or we undertransfuse them. It’s very hard to get it exactly right. And I think there are as many detrimental things done to the patient when you over-resuscitate. Abdominal compartment syndrome, pulmonary edema, peripheral compartment syndromes and all the sequelae they cause. But I think it’s equally detrimental when you under-resuscitate the patient as well. I think we all know that as well. So the real question is: How do we best communicate across the various specialties that are managing the patients? I think that is the real answer that we need to focus some of our attention on.

Dr. Malone: I think it has to be a team effort to correctly transfuse the patient.

Dr. Grathwohl: That’s the key, absolutely. It’s a dynamic conversation between the people that are giving the blood products and the surgeon and the patient. The patient tells you a lot of information. And I think that’s the key.

Dr. Grathwohl: Is there evidence to support any of the recommendations that you presented?

Dr. Malone: There is both anecdotal practice information and scientific evidence. For each of these particular components of the protocol, we did a literature search. So there is data to support trying to correct hypothermia, coagulopathy, and so on. There is an abundance of data suggesting that dilution is an unrecognized and major problem. There is support for the use of blood product ratios as related to avoidance of dilution.