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CRITICAL CARE

Role of the massive transfusion protocol in the management of haemorrhagic shock

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Editor's key points

- Retrospective data from victims of severe military trauma have led to fixed blood component ratio therapy in trauma.
- Close inspection of these studies reveals important limitations in their interpretation including a prominent effect of survivor bias.
- Point-of-care viscoelastic testing of whole blood coagulation provides an individualized approach to therapy to reduce unnecessary plasma transfusion.

The concept of rapid delivery of multiple blood products to the bedside of a massively haemorrhaging patient seems to be a logical approach to the management of the massively bleeding patient. However, controversy exists in the use of fixed blood component ratios. Assessing the extent of the coagulopathy through point-of-care testing might provide patients with product administration as needed, and avoid excessive transfusion and its associated complications.

Keywords: blood component transfusion; consumption coagulopathy; erythrocytes; trauma

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From the experience gained during the Iraq and Afghanistan conflicts, a concept of damage control resuscitation has arisen. Within the context of damage control resuscitation is the incorporation of the massive transfusion protocol, which dictates that blood is delivered expeditiously to the bleeding patient, generally in a fixed ratio. The protocol is intended to provide blood to the patient bedside in a rapid fashion. At the author's institution for example, 10 units of O+ uncross-matched packed red blood cell (RBC) units, 6 units of AB plasma, and 2 bags of platelets are provided.

The importance of the ratio of these products is where controversy arises. Some evidence, which will be discussed, implies that these products should be administered in a fixed ratio of 1 unit of packed erythrocytes to 1 unit of plasma to 1 unit of platelets (generally termed the 1:1:1 transfusion ratio). Most of these studies focus primarily on the erythrocyte to plasma ratio so in reality, this discussion primarily entails a 1:1 erythrocyte:plasma transfusion ratio. In 1982, the phrase 'viscious circle of trauma' was coined, which refers to the acidosis, hypothermia, and coagulopathy of trauma.[1] The intent of aggressive plasma use is to address the coagulopathy of trauma at an early stage. The following discussion is an unsystematic review of literature related to the fixed ratio plasma to red cell transfusion strategy.

Fixed ratio transfusion

The evidence for a 1:1 transfusion ratio derives from a number of studies. The landmark study that started this practice was by Borgman and colleagues in 2007.[2] This was a retrospective chart review of massive transfusion at a US Army combat support hospital. Massive transfusion was defined as >10 RBC units in 24 h. They separated 246 patients into three groups, depending on the ratio of RBCs to plasma. High plasma patients who received high ratios of plasma units to RBCs had higher survival rates compared with those who received a low ratio of plasma units to RBCs. From this non-randomized, retrospective analysis, the authors concluded that a higher ratio of plasma to erythrocytes contributed to a better outcome. What seems to have been neglected in the analysis was that the patients who received the high ratio had lower rates of thoracic and head injuries; had haemoglobin concentrations on presentation to the combat hospital that were 1.5 gm dl^{-1} higher than the low ratio group; had reduced base deficit (8 compared with the low ratio group with a base deficit of 13); and had a lower International normalized ratio (INR) of 1.54 compared with the low ratio group whose INR was 1.78. So, the low ratio group was more acidotic, more coagulopathic, and more anaemic than the high ratio group. In addition, for the patients who died in the low ratio group, they did so at an average of 2 h from arrival into the combat facility; whereas, the patients in the high ratio group died on average at 37 h and died more commonly from sepsis, multi-organ failure, and central nervous system injury.

A number of studies similar in study design followed the Borgman study (see Table 1). In 2008, a retrospective civilian study involving 16 level I trauma centres and 467 patients was published,[5] which also found improved survival with higher ratios of plasma and platelets. This study appeared to be the catalyst for many trauma surgeons to adopt the 1:1 transfusion strategy. Like the Borgman study, there were

stark differences in time-to-death between the patients that received high ratios of plasma and platelets. If the time of death and the average number of blood products administered to the patients who died in each group are used to estimate rates of blood product administration between ratio groups, stark differences in patient populations appear to exist in this study also. Patients who were categorized in a low plasma, low platelet group, received erythrocytes at a rate of 5.25 units per hour before death whereas for the high plasma, high platelet group erythrocytes were given at a rate of 0.63 units per hour (Table 2). Additionally, the mechanism of injury was truncal and head injury in 58% of the low ratio patients and 23% in the high ratio patients. While this study has been highly influential, caution would be suggested in translating these findings to civilian trauma.

Each of the studies outlined in Table 1 has flaws associated with their retrospective study design. Most prominently, survivor bias has been a repetitive source of error in these 1:1 ratio studies. Survivor bias is associated with having survived long enough to receive a particular therapy. A nice example to illustrate this bias is shown in Figure 1. In Figure 1A, four erythrocyte units are administered to a patient followed by a plasma unit, at which point the patient dies. In Figure 1B, the same pattern of blood administration occurred; however, the patient did not die and was given further plasma units before the end of resuscitation. So, the short survival patient in Figure 1A received an erythrocyte:plasma ratio of 4:1 (low ratio); whereas the surviving patient in Figure 1B received a 1:1 ratio of erythrocyte to plasma (high ratio). This illustrates survivor bias in that the only real difference is that the patient in Figure 1A simply died earlier whereas the therapy was identical up until that point.

To assess the effect of survivor bias, Snyder and colleagues[12] looked at the impact of a high ratio of plasma to RBCs compared with a low ratio (Table 3). In this study, 40% of the high ratio patients died while 58% of the low ratio patients died. However, if one looks at the time of death, there is clearly a difference between groups. Like the aforementioned studies, the low ratio group patients died much earlier in their care. When Snyder and colleagues looked at the relative risk of death with a time-varying covariate, the survival advantage of the added plasma disappeared, thus confirming the existence of this bias.

Effect of plasma on coagulation function

Many of the studies outlined in Table 1 report average INR values that are mildly or slightly elevated, generally around an INR of 1.8. While there is no debate that trauma is associated with coagulopathy, there is substantial evidence that transfusing plasma in circumstances where the INR is minimally elevated has a minimal effect on the INR.[15–17] While minimal effect on INR occurs, it does expose the patient to risks associated with plasma transfusion.[18] These risks primarily relate to acute allergic reactions,[19] transfusion related acute lung injury,[20 21] and transfusion associated circulatory overload.[22]

Part of this minimal effect relates to the variable procoagulant potency of transfused plasma. The INR of transfused plasma ranges from <1 to >1 based on the donor and the effect of storage. Some plasma can have an INR as high as 1.3.[23] So, if an INR level is <1.3, there is a good chance that plasma transfusion will raise the INR. In addition, correction of an INR is not linear and at low INR values, plasma has little effect.[24 25] If plasma is given to raise coagulation factor concentrations by 10%, the effect will be very different depending upon the starting INR. For instance, if the INR is 1.5 and enough plasma is given to raise factor concentrations by 10%, then the result will be to correct it to 1.4. A similar change in 10% when the INR is 3.0 will result in a new INR of 2.3, so the effect is much greater at higher INRs. Recent evidence suggests that conventional laboratory tests of coagulation are insensitive in detection acquired coagulopathy as in trauma, or in guiding procoagulant therapy.[26 27]

With the understanding that varying effects of plasma transfusion are seen at varying INR values, what is necessary to raise the INR level by 10%? First, each plasma unit varies in volume depending on how it is collected and the haematocrit of the donor. In general, each unit contains 250 ml with each millilitre of plasma containing one unit of procoagulant activity. Since the procoagulant content of a unit of plasma is diluted by anticoagulant and since some activity is lost in processing, a 250 ml unit of plasma might be expected to provide $\sim$200 units of procoagulant activity on average. Recovery of procoagulant factors in plasma is not 100%, however, and may be as low as 20–40%. Thus, in a 70 kg patient with a 3000 ml plasma volume, transfusion of one 250 ml unit of plasma might be expected to increase most factors by $\sim$2.5% (or 0.025 U ml^{-1}). Transfusion of four units would raise levels by $\sim$10%. The 1:1 RBC: plasma ratio is predicated on correction of one arm of the lethal triad of trauma (acidosis, hypothermia, and coagulopathy). Administration of 1 unit of plasma to treat mildly abnormal INR elevations would be anticipated to have little to no effect on coagulation function while exposing the patient to the adverse effects of plasma.

Adverse effects of aggressive plasma use

Logically, it would seem that more plasma would facilitate resuscitation early in the hospital course of a trauma patient, but the question must be asked as to whether such aggressive plasma use simply facilitates resuscitation that could be achieved with a different colloid solution such as albumin. If this better resuscitation is facilitated, is there harm that could potentially arise from aggressive plasma use compared with an alternate therapy.

Several investigators have attempted to answer this question. Perel and colleagues,[28] in a secondary analysis of the CRASH-2 (clinical randomization of an antifibrinolytic in significant haemorrhage 2) trial data (a study to assess the impact of tranexamic acid in trauma patients), found that transfusion increased the survival in a patient population where 50% of the patients were predicted to die; whereas