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+ uncrossmatched 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 ‘vicious circle of trauma’ was coined, which refers to the acidosis, hypothermia, and coagulopathy of trauma. 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. 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 acidic, more coagulopathic, and more anaemic than the high ratio group.

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, 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 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. While minimal effect on INR occurs, it does expose the patient to risks associated with plasma transfusion. These risks primarily relate to acute allergic reactions, transfusion related acute lung injury, and transfusion associated circulatory overload.

Part of this minimal effect relates to the variable procoagulant potency of transfused plasma. The INR of transfused plasma ranges from <1 to 1.3. 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. 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.

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 ~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 ~2.5% (or 0.025 U ml⁻¹). Transfusion of four units would raise levels by ~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, in a secondary analysis of the CRASH-2 (clinical randomization of an antifibrinolytic in significant hemorrhage 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
Table 1  Studies advocating 1:1 transfusion ratios. PRBC, packed red blood cells. NR, not reported; FFP, plasma; PRBC, erythrocytes; TEP, transfusion exsanguination protocol; MT, massive transfusion; MTP, massive transfusion protocol; LOS, length of stay; MOF, multiple organ failure; ARDS, acute respiratory distress syndrome.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Interventions</th>
<th>Control</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borgman, 2007</td>
<td>Retrospective, cohort</td>
<td>NR</td>
<td>FFP:PRBC ratios from 1:8 to 1:2.5</td>
<td>FFP:PRBC ratio 1:1.4</td>
<td>High FFP, lower death</td>
</tr>
<tr>
<td>Cotton, 2008</td>
<td>Non-randomized pre-post</td>
<td>30 days</td>
<td>TEP (PRBC:FFP:Plts 10:4:2)</td>
<td>No TEP less FFP, also needed &gt; 10 units PRBC in first 24 h</td>
<td>TEP reduced death</td>
</tr>
<tr>
<td>Cotton, AAST, 2008</td>
<td>Non-randomized pre-post</td>
<td>NR</td>
<td>TEP (PRBC:FFP 3:2)</td>
<td>No TEP, less FFP</td>
<td>TEP reduced MOF</td>
</tr>
<tr>
<td>Gunter, 2008</td>
<td>Non-randomized pre-post</td>
<td>30 days</td>
<td>PRBC:FFP 3:2 or greater</td>
<td>PRBC:FFP 3:2 or less</td>
<td>High FFP, lower death</td>
</tr>
<tr>
<td>Holcomb, 2008</td>
<td>Retrospective cohort</td>
<td>30 days</td>
<td>High plasma to PRBC ≥ 1:2</td>
<td>Low plasma to PRBC &gt; 1:2</td>
<td>High FFP, lower death</td>
</tr>
<tr>
<td>Duchesne, 2008</td>
<td>Retrospective cohort</td>
<td>Death</td>
<td>High plasma to PRBC &gt; 1:2</td>
<td>Low plasma to PRBC &gt; 1:2</td>
<td>High FFP, lower death</td>
</tr>
<tr>
<td>Kashuk, 2008</td>
<td>Retrospective cohort</td>
<td>Death, or LOS</td>
<td>FFP:PRBC ratios from 1:1 to 1:4</td>
<td>FFP:PRBC ratio 1:5</td>
<td>No benefit</td>
</tr>
<tr>
<td>Moore, 2008</td>
<td>Prospective cohort,</td>
<td>Death, or LOS</td>
<td>MT protocol, subgroups of early, late death, survivors</td>
<td>No MT</td>
<td>MT provides better outcomes</td>
</tr>
<tr>
<td>Scalea, 2008</td>
<td>Prospective, cohort</td>
<td>Death, or LOS</td>
<td>Transfusion, stratification by ratio</td>
<td>No transfusion</td>
<td>No benefit</td>
</tr>
<tr>
<td>Sperry, 2008</td>
<td>Prospective, cohort</td>
<td>Death, or LOS</td>
<td>PRBC:FFP &lt; 1:1.5</td>
<td>PRBC:FFP &gt; 1:1.5</td>
<td>High FFP, lower death, higher ARDS</td>
</tr>
<tr>
<td>Dente, 2009</td>
<td>Prospective, cohort</td>
<td>30 days</td>
<td>MTP 1:1:1</td>
<td>No MTP</td>
<td>Reduces short-term mortality but no difference at 30 days</td>
</tr>
<tr>
<td>Snyder, 2009</td>
<td>Retrospective, cohort</td>
<td>Death, or LOS</td>
<td>Survivors</td>
<td>Non-survivors</td>
<td>PRBC:FFP ratio predictive of death but survival bias negated effect</td>
</tr>
<tr>
<td>Zink, 2009</td>
<td>Retrospective, cohort</td>
<td>30 days</td>
<td>PRBC:FFP 1:1</td>
<td>PRBC:FFP &gt; 1:1</td>
<td>Survival better in 1:1</td>
</tr>
<tr>
<td>Teixeira, 2009</td>
<td>Retrospective, cohort</td>
<td>Death, or LOS</td>
<td>PRBC:FFP 1:1</td>
<td>PRBC:FFP in lower ratios</td>
<td>Survival better in 1:1</td>
</tr>
</tbody>
</table>
plasma transfusion increased the risk of death in a cohort of patients that had a predicted risk of death < 20%. Similarly, Inaba and colleagues found an association between plasma use and overall complications in non-massively transfused patients (defined as patients receiving < 10 units of PRBCs during the first 24 h of their hospitalization). In a retrospective review of 1440 trauma patients, Johnson and colleagues found an increased risk of multiple organ failure when patients were transfused aggressively with plasma. These authors suggested that caution is warranted when empirically transfusing plasma. These three studies suggest that in the bleeding patient, more plasma might have unpredictable results when given using a fixed ratio strategy.

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**Table 2: Blood component transfusions by plasma and platelet ratios. Reproduced with permission from Holcomb and colleagues.**

<table>
<thead>
<tr>
<th></th>
<th>High plasma, High Platelets</th>
<th>High plasma, low platelets</th>
<th>Low plasma, high platelets</th>
<th>Low plasma, low platelets</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma (units)</td>
<td>17 (12)</td>
<td>16 (10)</td>
<td>7 (5)</td>
<td>6 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets (units)</td>
<td>20 (16)</td>
<td>5 (6)</td>
<td>18 (10)</td>
<td>4 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RBC (units)</td>
<td>22 (17)</td>
<td>21 (12)</td>
<td>21 (11)</td>
<td>21 (12)</td>
<td></td>
</tr>
<tr>
<td>Crystalloid (L)</td>
<td>14 (10)</td>
<td>13 (7)</td>
<td>17 (12)</td>
<td>11(10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FFP:RBC ratio</td>
<td>0.8 (0.3)</td>
<td>0.8 (0.3)</td>
<td>0.3 (0.1)</td>
<td>0.2 (0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet:RBC ratio</td>
<td>0.9 (0.4)</td>
<td>0.2 (0.2)</td>
<td>0.9 (0.4)</td>
<td>0.1 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Crystalloid:RBC ratio</td>
<td>0.8 (0.5)</td>
<td>0.8 (0.6)</td>
<td>0.9 (0.6)</td>
<td>0.6 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Received rFVIIa (%)</td>
<td>34 (22)</td>
<td>11 (11)</td>
<td>21 (25)</td>
<td>15 (12)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

**Table 3: Group sizes* and numbers of deaths in low (<1:2) and high (>1:2) FFP:PRBC ratio groups by time interval of hospitalization. Reproduced with permission from Snyder and colleagues.**

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>≤30 min.</th>
<th>&gt;30–60 min.</th>
<th>&gt;60–90 min.</th>
<th>&gt;90–120 min.</th>
<th>&gt;2–3 hrs.</th>
<th>&gt;3–4 hrs.</th>
<th>&gt;4–5 hrs.</th>
<th>&gt;5–6 hrs.</th>
<th>&gt;6–12 hrs.</th>
<th>&gt;12–18 hrs.</th>
<th>&gt;18–24 hrs.</th>
<th>&gt;24 hrs.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1:2 (low ratio)</td>
<td>86</td>
<td>102</td>
<td>103</td>
<td>102</td>
<td>95</td>
<td>91</td>
<td>85</td>
<td>87</td>
<td>74</td>
<td>73</td>
<td>74</td>
<td>74</td>
<td>43</td>
</tr>
<tr>
<td>No. pts in group</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>No. deaths during interval</td>
<td>1</td>
<td>6</td>
<td>13</td>
<td>20</td>
<td>34</td>
<td>39</td>
<td>46</td>
<td>46</td>
<td>60</td>
<td>61</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>&gt;1:2 (high ratio)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>13</td>
<td>24</td>
</tr>
</tbody>
</table>

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**Fig 1** Survivor bias. (A) a theoretical patient receives 4 erythrocyte units followed by a plasma unit and subsequently dies, so a 4:1 ratio results. (B), a theoretical patient receives 4 erythrocyte units followed by 4 plasma units but doesn’t die resulting in a 1:1 ratio. The therapy is identical with the exception being the death of the patient.
Laboratory-guided plasma use

In order to avoid excessive or overzealous administration of blood products, several investigators now suggest that transfusion be guided by laboratory testing. In a randomized study, Nascimento and colleagues31 compared a fixed transfusion ratio with transfusion guided by laboratory data every 2 h. This study enrolled 78 patients with the primary aim being to assess the feasibility of doing a larger study of this topic. They found a trend towards worse outcomes with the fixed ratio strategy of care compared with laboratory-guided plasma and platelet use, but concluded that a larger study size was needed in order to show statistical significance. Regardless, the authors make a significant leap in sophistication from the recipe of giving blood products in a fixed ratio to one that is guided by laboratory data.

Traditional laboratory testing provides slow information by which to make a care decision but the concept of point-of-care testing allows for rapid testing and resulting of coagulation data at the point of the patient bedside. This appears to be the direction that the literature is evolving as it relates to the massively bleeding patient. Point-of-care devices that have been used for this purpose include the thromboelastograph (Haemonetics, Inc., Braintree, MA, USA), the Rotem (TEM, Munich, Germany), and the Sonoclot (Sienco, Inc., Boulder, CO, USA). Each of these devices measures viscoelastic changes in whole blood as it clots. Changes in fibrinogen, platelets, and coagulation factors influence the result from these devices so that goal-directed therapy can be achieved. Multiple investigators have now shown improved outcomes when using a goal-directed strategy of transfusion compared with fixed ratio strategies.32–35

Similar conclusions have been demonstrated in cardiac surgery where it has been demonstrated that when plasma and platelet transfusions are guided by thromboelastography, better patient outcomes with fewer blood products result.5–6,36–37 The evidence appears compelling in cardiac surgery to the point that national guidelines have been developed suggesting that point-of-care testing be used for guidance of transfusion.38 It would seem reasonable that the cardiac patient is similar enough to the massively bleeding patient that these guidelines could be extrapolated to the trauma patient. Recently, a multidisciplinary task force for advanced bleeding care in trauma concurred with the recommendation that viscoelastometry be used for guiding transfusion.39

Conclusions

The concept of rapid delivery of multiple blood products irrespective of their specific ratio—to the bedside of a massively haemorrhaging patient seems to be a logical approach to management only if a pathophysiology-oriented point-of-care-guided management cannot be applied. Hyperfibrinolysis can be treated with anti-fibrinolytic drugs or hypofibrinoinaemia with cryoprecipitate or fibrinogen concentrate rather than plasma transfusion. Studies of plasma use suggest that the immediate benefits of plasma transfusion only outweigh the risks when a coagulopathy is severe. However, overall risks increase with escalating plasma exposure, thus affecting patient safety. Assessing the extent of coagulopathy through conventional laboratory testing cannot help guide bleeding management, but minor derangements in routine coagulation tests can be used to avoid excessive allogeneic blood transfusions including plasma and its associated complications. Future prospective research is warranted to assess the potential benefits of rapid delivery of plasma in a fixed ratio to RBC concentrates compared with laboratory testing guided plasma without a fixed ratio to other blood products compared with individualized coagulation management based on point-of-care coagulation monitoring.

Declaration of interest

None declared.

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