

# High Transfusion Ratios Are Not Associated With Increased Complication Rates in Patients With Severe Extremity Injuries

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**Background:** High transfusion ratios of plasma to packed red blood cells ( $>1:2$ ) have been associated with increased survival and increased complications in patients receiving massive transfusion (MT). We hypothesized that high ratio transfusion would be associated with no survival benefit and increased complications in combat victims with compressible hemorrhage.

**Methods:** A retrospective analysis of soldiers injured in the current conflict during 5 years ( $n = 2,105$ ) who received blood was performed on those with isolated extremity (abbreviated injury scale extremity score  $\geq 3$  and abbreviated injury scale score 0–2 in all other regions) injury comparing those who received a MT with those who did not. Transfusion ratios in the first 24 hours were correlated with outcomes.

**Results:** Injury severity score (14.6 vs. 12.1;  $p < 0.05$ ), international normalized ratio (1.65 vs. 1.28;  $p < 0.05$ ), and base deficit (8.0 vs. 3.7;  $p < 0.05$ ) were higher in the MT group. High transfusion ratios were associated with a trend toward decreased mortality (17.2% vs. 6.9%;  $p = 0.07$ ) in MT patients and no increased complications (20.7% vs. 26.4%;  $p > 0.05$ ). In those receiving a non-MT, high ratios were associated with similar mortality (4.8% vs. 3.9%;  $p > 0.05$ ) and complications (12.4% vs. 9.2%;  $p > 0.05$ ).

**Conclusions:** Extremity injured patients receiving MT may benefit from high transfusion ratios and do not experience increased complications. No change in mortality or complications was observed in non-MT patients across transfusions ratios. High transfusion ratios are not associated with increased complications in patients with isolated extremity injury regardless of whether a MT is required.

**Key Words:** Extremity injury, Damage control resuscitation, Combat injuries.

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Hemorrhage is the primary cause of potentially survivable death in combat trauma patients. High-energy penetrating mechanisms of injury such as improvised explosive

devices, rocket-propelled grenades, and high-velocity rifles are responsible for an increase in number and severity of wounds in combat.<sup>1,2</sup> Recent data show that patients who receive a massive transfusion (MT;  $\geq 10$  units packed red blood cells [PRBC] in 24 hours) benefit from a high transfusion ratio, defined in the literature as a goal ratio of 1:1 of fresh frozen plasma (FFP) to PRBC.<sup>3–5</sup>

Injuries sustained in combat trauma can be classified as compressible or noncompressible. Compressible injuries primarily involve the extremities. Extremity hemorrhage can be effectively treated with external measures such as direct pressure, application of a tourniquet, or the use of advanced hemostatic dressings.<sup>6</sup> Noncompressible injuries involve body cavities (chest, abdomen, and pelvis). Bleeding from these areas cannot be controlled with external measures, and patients must be taken to the operating room for definitive management.<sup>1,2,7</sup>

High ratios of FFP to PRBC are associated with decreased mortality in patients who are massively transfused. However, these high ratios are also associated with a concurrent increase in morbidity.<sup>5</sup> This effect of decreased mortality and increased morbidity is thought to partially result from survivor bias.<sup>8</sup> Those patients receiving high-ratio MTs who survive their combat injuries are alive to suffer complications later in their hospital course.

The compressibility of the combat injury also affects the treatment strategy used by combat theater medical providers. Because compressible injuries can be controlled by external measures, there may be limited benefit of high-ratio transfusion. In contrast, patients with noncompressible injuries have no effective external treatment; a high-ratio MT strategy may be the best temporizing therapy before surgery.<sup>3,7</sup>

In this study, we compared the effect of transfusion ratios on combat trauma patients with isolated severe extremity injuries. We hypothesized that in combat victims with extremity injuries, high-ratio transfusions were associated with equivalent survival and increased complications compared with lower ratios.

## PATIENTS AND METHODS

A retrospective analysis of combat victims injured during the current conflict (March 2003 to June 2008) was performed. Only those patients receiving at least one unit of PRBC were included in the analysis. The protocol was approved by the Institutional Review Board at Brooke Army Medical Center. A database was created, including demographics, admission vital signs, admission laboratories, injury

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severity score, abbreviated injury scale (AIS) score by body regions, initial Glasgow coma scale score, mortality, overall complication rate, use of recombinant factor VIIa (rFVIIa), and specific complications [myocardial infarction, cerebrovascular accident, deep venous thrombosis, pulmonary embolus (PE), acute respiratory distress syndrome, and acute renal failure (ARF)]. Isolated extremity injured (EI) patients were defined as those with an AIS extremity score  $\geq 3$  and an AIS score of 0 to 2 in all other AIS regions (head, face, chest, abdomen, and external).

Patients were divided into three groups based on their transfusion ratio. A low transfusion ratio was defined as less than a 1:4 ratio of FFP to PRBC. A mid transfusion ratio ranged from greater than or equal to a 1:4 ratio of FFP to PRBC up to and including a 1:2 ratio of FFP to PRBC. A high transfusion ratio included patients who received greater than a 1:2 ratio of FFP to PRBC. The transfusion ratio was determined at 24 hours postadmission. MT was defined as transfusion of greater than 10 units of PRBC in 24 hours. Because the study population consisted of military personnel, fresh whole blood (FWB) was available and used for transfusion. One unit of FWB is considered to be equivalent to one unit of PRBC and one unit of FFP. Total PRBCs given were calculated by adding PRBC units and one unit of PRBC from each unit of FWB transfused. The transfusion ratio was calculated by including a unit of FFP and PRBC per unit of FWB used. All statistical analyses were performed using SAS 9.1.3 (SAS Institute, Cary, NC). Student's *t* test and  $\chi^2$  analysis were used as appropriate with  $p < 0.05$  as statistically significant.

## RESULTS

Data were obtained from 2,105 injured soldiers who received at least one unit of PRBC. Any patients who had missing data for a given variable were excluded from analysis for that variable. The admission characteristics and demographics of the EI patients are shown in Table 1. No significant difference is seen between age and admission temperature. However, significant differences are seen among heart rate, systolic blood pressure, injury severity score, Glasgow coma scale score, admission hemoglobin, international normalized ratio, and base deficit, with the MT group appearing more critically ill.

**TABLE 1.** Patient Characteristics

| Extremity Injury               | MT    | Non-MT |
|--------------------------------|-------|--------|
| Age                            | 25.7  | 25.8   |
| Heart rate                     | 117*  | 98.7   |
| Temperature (°F)               | 97.6  | 98.2   |
| Systolic blood pressure        | 109*  | 121    |
| Injury severity score          | 14.6* | 12.1   |
| Glasgow coma scale score       | 12.7* | 14.1   |
| Hemoglobin                     | 11.2* | 12.2   |
| International normalized ratio | 1.65* | 1.28   |
| Base deficit                   | 8.0*  | 3.7    |

\*  $p < 0.05$ .

## Massive Transfusion

For the massively transfused combat trauma patients, mortality and complications were compared across transfusion ratio groups (Table 2). This subgroup represents the most critically injured patients because they received more than 10 units of PRBC in 24 hours. There was no difference in mortality or morbidity across the ratio groups (Table 2).

Specific complication data, including the incidence of myocardial infarction, cerebrovascular accident, PE, deep venous thrombosis, ARF, and acute respiratory distress syndrome, are shown in Table 2. In EI patients, only ARF was significantly different when comparing the low to high transfusion ratio group (13.8% vs. 3.5%;  $p < 0.05$ ).

## Nonmassive Transfusion

Mortality and complication rates were compared across ratios in patients who did not receive a MT (Table 3). Mortality and morbidity were the same across ratio groups in EI patients. EI patients receiving low transfusion ratios had a significantly lower rate of PE when compared with the mid and high ratio groups.

## Use of Recombinant Factor VIIa

The use of rFVIIa was uniformly more frequent in the high ratio transfusion group (Table 4).

## DISCUSSION

The most common cause of preventable combat-related death is hemorrhage. Development of the lethal triad (acidosis, hypothermia, and coagulopathy) exacerbates the mortality rate.<sup>9,10–16</sup> Prompt recognition of hemorrhage and treatment with an appropriate transfusion strategy or surgical intervention is essential to improve survival. Several retrospective studies have shown improved outcomes associated with transfusion of FFP, platelets, and PRBC in a 1:1:1 ratio in severely injured patients receiving a MT.<sup>3–5,8,15–25</sup> Because recent data show that aiming for a goal ratio of 1:1 achieves an actual ratio of 1:2 in 98% of patients,<sup>3</sup> we defined the high ratio group as greater than a 1:2 ratio of FFP to PRBC. The use of high ratios of FFP and platelets to PRBC in MT is commonly known as hemostatic or damage control resuscitation.

**TABLE 2.** Massive Transfusion

| Parameter                               | Extremity Injury             |                                     |                                |
|-----------------------------------------|------------------------------|-------------------------------------|--------------------------------|
|                                         | Low<br>( $<1:4$ ),<br>n = 29 | Mid<br>( $1:4$ – $1:2$ ),<br>n = 59 | High<br>( $>1:2$ ),<br>n = 159 |
| Mortality (%)                           | 17.2                         | 8.5                                 | 6.9                            |
| Overall complications (%)               | 20.7                         | 15.3                                | 26.4                           |
| Myocardial infarction (%)               | 0.0                          | 0.0                                 | 0.6                            |
| Cerebrovascular accident (%)            | 0.0                          | 0.0                                 | 0.6                            |
| Pulmonary embolus (%)                   | 3.6                          | 5.1                                 | 9.4                            |
| Deep venous thrombosis (%)              | 10.3                         | 8.5                                 | 13.2                           |
| Acute renal failure (%)                 | 13.8*                        | 3.1                                 | 3.5                            |
| Acute respiratory distress syndrome (%) | 10.3                         | 5.1                                 | 5.7                            |

\*  $p < 0.05$  when comparing low to high ratio.

TABLE 3. Nonmassive Transfusion

| Parameter                               | Extremity Injury          |                             |                            |
|-----------------------------------------|---------------------------|-----------------------------|----------------------------|
|                                         | Low<br>(<1:4),<br>n = 283 | Mid<br>(1:4–1:2),<br>n = 68 | High<br>(>1:2),<br>n = 105 |
| Mortality (%)                           | 3.9                       | 2.9                         | 4.8                        |
| Overall complications (%)               | 9.2                       | 8.8                         | 12.4                       |
| Myocardial infarction (%)               | 0.0                       | 0.0                         | 0.0                        |
| Cerebrovascular accident (%)            | 0.0                       | 0.0                         | 0.0                        |
| Pulmonary embolus (%)                   | 1.4*†                     | 6.0                         | 6.7                        |
| Deep venous thrombosis (%)              | 5.3                       | 6.0                         | 2.9                        |
| Acute renal failure (%)                 | 1.4                       | 1.5                         | 1.9                        |
| Acute respiratory distress syndrome (%) | 2.5                       | 3.0                         | 2.9                        |

\*  $p < 0.05$  when comparing low to mid ratio.†  $p < 0.05$  when comparing low to high ratio.

TABLE 4. Recombinant Factor VIIa Use

| Parameter                | Extremity Injury (EI) |                  |                |
|--------------------------|-----------------------|------------------|----------------|
|                          | Low<br>(<1:4)         | Mid<br>(1:4–1:2) | High<br>(>1:2) |
| n                        | 29                    | 59               | 159            |
| rFVIIa use (%) in MT     | 27.6                  | 17.0‡            | 47.2           |
| n                        | 283                   | 68               | 105            |
| rFVIIa use (%) in non-MT | 1.4*†                 | 8.8              | 16.2           |

\*  $p < 0.05$  when comparing low to mid ratio.†  $p < 0.05$  when comparing low to high ratio.‡  $p < 0.05$  when comparing mid to high ratio.

Hemorrhage from extremity injuries is treated effectively with direct pressure, application of tourniquets, use of advanced hemostatic dressings, and definitive surgery. For this reason, we hypothesized that high ratio transfusion would not improve outcomes. Although mortality was not significantly different between EI patients receiving high and low ratios, the possibility of a type 1 error exists as mortality in the high ratio group was less than half of that in the low ratio group. Similarly, in those patients who did not receive a MT, there was no difference in survival across ratio groups.

The overall rate of complications across ratio groups did not differ significantly in the MT and non-MT patients. However, the low ratio MT group suffered a significantly higher rate of ARF when compared with the high ratio group (13.8% vs. 3.8%;  $p < 0.05$ ). This low ratio MT group may have developed renal failure secondary to rhabdomyolysis as a result of their extremity injury. Alternatively, the etiology of ARF may be simply from inadequate resuscitation. In the non-MT population, the mid and high ratio groups had a significantly higher percentage of PE when compared with the low ratio group (Table 3). A higher percentage of the mid and high ratio groups received rFVIIa possibly contributing to the development of thrombotic complications.

There are several limitations to this study. Because this study is retrospective, only associations can be made. Not all data points were available for analysis in each patient. When this was the case, the data point in question was excluded from

analysis. In addition, the manner in which extremity injuries were treated was not included in the database. Given these limitations, future analyses should include a multivariate analysis to account for baseline differences between groups.

In conclusion, isolated extremity injuries with compressible hemorrhage may benefit from high ratios of FFP to PRBC if a MT is required. Achieving high ratio transfusions is not associated with an increase in overall complications, independent of MT. However, because all existing data on damage control resuscitation has been gathered retrospectively, a prospective randomized trial is overdue.

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## DISCUSSION

**Juan C. Duchesne** (Tulane University, New Orleans, LA): First, I would like to thank the ATACCC (Advanced Technology Applications for Combat Casualty Care) for facilitating and creating key bridges of communication between the military and the civilian population. Meetings like this one will improve our current management and outcomes of trauma patients. I would like to commend the authors for allowing me to review their work way ahead of time prior to this meeting and for their interest in the modality of damage control resuscitation.

In their work titled “High transfusion ratios are not associated with increased complication rates in patients with severe extremity injuries,” the authors hypothesized that a high ratio transfusion (close ratio) would be associated with increased complications in combat victims with compressible hemorrhage and those who do not require massive transfusion (MT). Their study was a retrospective analysis of soldiers injured over 5 years who received blood. They compared outcomes in patients with isolated extremity injury based on transfusion ratios. In their results, extremity injury (EI) patients with high transfusion ratios were associated with a trend toward decreased mortality in MT patients and a trend toward increase in complications but of no statistical significance. They conclude that close ratio resuscitation doesn’t impact outcomes in patients with EI.

I have several questions and comments for the authors:

1. Regarding severe hemorrhage definition, a patient that receive >10 units over 24 hours are not the same as those that receive >10 units in the Operating room. Can you comment on why we are still stuck with looking into patients with >10 units over 24 hours and not during the OR. How will this change in definition impact your outcomes?
2. Your study uses as a reference the work of Snyder regarding the relationship of blood product ratio to mortality: survival benefit or survival bias? It relates an increase in

complications with close ratio resuscitation. We don’t see this trend in complications at Charity New Orleans where our MTP is 6.2%/year with an inverse ratio of penetrating to blunt of 59% to 41%. Please help us clarify why this dataset doesn’t correlate with “down in the trenches” clinical outcomes. What am I missing?

3. Why were TBI patients included in your analysis? Head injury is an independent predictor of increase mortality and morbidity and increase in LOS. This group should be excluded in order to provide better transparency, and if not, adjusting with a logistic regression will help to clarify this selection bias. Your selection bias is hurting your outcomes.
4. Why were patients transfused with FWB included in your analysis? Assuming one unit of FWB is considered to be equivalent to one unit of PRBC and one unit of FFP is a bad generalization. Component resuscitation conveys a dilution factor. 500 cc of fresh whole blood compares to 660 cc of 1:1:1 PRBC/FFP/Plt as follows: Hct of 30 to 44% vs. 29%, Plt count of 150 to 400 vs. 87, coagulation activity of 100% vs. 65% and fibrinogen of 1.5 gms vs. 750 mgs.
5. Transfusion ratios don’t impact mortality in extremity injuries with severe hemorrhage. In other words, the chances of dying from a brachial artery blood donation is not equivalent to the same amount of blood loss from severe tissue injury in the presence of tissue hypoperfusion. I strongly believe the use of tourniquets was the key factor here. Can you please provide us how many patients had tourniquets in place? In the civilian setting we are still adjusting the mentality of our EMS in order to save these compressible bleeders, but we are doing poorly. These groups of patients often arrive with hard to correct advance Trauma Induced Coagulopathy.
6. The last time we used factor 7 at our institution since institution of DCR was more than a year ago. Before DCR factor 7 was always use as our bail out drug to stop TIC . . . in your study factor 7 utilization increased within the group of patients with close ratio resuscitation . . . please explain how this happened? I found it hard to understand this, especially when you are achieving effective early hemostatic resuscitation in your patients.

Once again, I will like to commend the authors for their work.

**Philbert Van** (Oregon Health & Science University, Portland, OR): Thank you, Dr. Duchesne, for those insightful comments and questions.

1. I agree with you regarding the fact that patients who receive greater than 10 units of PRBC while in the OR are more critically ill than those who receive more than 10 units over a 24-hour period. We are still stuck with the “greater than 10 units in 24 hours” definition because of the retrospective nature of these transfusion studies. Without more detailed and accurate data on the exact timing of blood product arrival and transfusion, it is very difficult to adopt the definition you are suggesting. However, if we

were able to use the “greater than 10 units while in OR” definition, I think there would be an increase in mortality and complications, as the subset of patients would be more ill, but there would still be no significant differences across ratio groups.

2. In this study, the patients in the high ratio transfusion group (regardless of massive transfusion) did not experience a statistically significant increase in complications, similar to your experience in New Orleans. Those receiving a high ratio transfusion did not gain any appreciable mortality benefit compared to the low ratio group. Therefore, the high ratio group is not surviving any longer to suffer more complications.
3. Inclusion of traumatic brain injury patients was one of the limitations of our study. This selection bias could have led to falsely elevated rates of mortality. In our future analyses, we plan to exclude those with a head AIS >1 and include logistic regression analyses.

4. The study population consisted of military personnel; therefore, fresh whole blood (FWB) was available for transfusion. We analyzed the data with and without the FWB patients, and there were no differences in the outcomes.
5. We also believe that use of external measures, such as the application of a tourniquet, resulted in decreased mortality in this study population. However, as mentioned in the discussion, the data set did not include specific information on whether or not a tourniquet was applied in treatment of the severe extremity injury.
6. During the time period of the study, the use of recombinant factor VIIa during damage control resuscitation was part of the military clinical practice guidelines along with high-ratio transfusions. The results of this study reflect those clinical practice guidelines.

Once again, I would like to thank the ATACCC Program Committee for the opportunity to present our research today.