

# Review of Current Blood Transfusions Strategies in a Mature Level I Trauma Center: Were We Wrong for the Last 60 Years?

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**Background:** Recent military experience reported casualties who receive >10 units of packed red blood cells (PRBC) in 24 hours have 20% versus 65% mortality when the fresh-frozen plasma (FFP) to PRBC ratio was 1:1 versus 1:4, respectively. We hypothesize a similar improvement in mortality in civilian trauma patients that require massive transfusion and are treated with a FFP to PRBC ratio closer to 1:1.

**Methods:** Four-year retrospective study of all trauma patients who underwent emergency surgery in an urban Level I Trauma Center. Patients were divided into two groups; those that received ≤10 units or >10 units of PRBC during and after initial surgical intervention. Only patients who received transfusion of both FFP and PRBC were included in the

analysis. The primary research question was the impact of initial FFP:PRBC ratio on mortality. Other variables for analysis included patient age, gender, mechanism, and Injury Severity Scale score. Both univariate and multivariate analysis were used to assess the relationship between outcome and predictors.

**Results:** A total of 2,746 patients underwent surgical intervention of which 1,985 (72.2%) received no transfusion. Of those that received transfusion, 626 (22.8%) received ≤10 units of PRBC and 135 (4.9%) >10 units of PRBC. Out of the 626 patients that received ≤10 units of PRBC, 250 (39.9%) received FFP and 376 (60.1%) received no FFP. All the patients that received >10 units PRBC received FFP. In univariate analysis, a significant difference in mortality was found in pa-

tients who received >10 units of PRBC (26% vs. 87.5%) when FFP:PRBC ratio was 1:1 versus 1:4 ( $p = 0.0001$ ). Multivariate analysis in the group of patients that received >10 units of PRBC showed a FFP:PRBC ratio of 1:4 was consistent with increased risk of mortality (relative risk, 18.88; 95% CI, 6.32–56.36;  $p = 0.001$ ), when compared with a ratio of 1:1. Patients who received ≤10 units of PRBC had a trend toward increased mortality (21.2% vs. 11.8%) when the FFP:PRBC ratio was 1:4 versus 1:1 ( $p = 0.06$ ).

**Conclusion:** An FFP to PRBC ratio close to 1:1 confers a survival advantage in patients requiring massive transfusion.

**Key Words:** Hemostatic Resuscitation, FFP:PRBC ratio, Civilian trauma, Outcomes, damage control resuscitation.

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Charity hospital situated in New Orleans, LA is a trauma center with more than 5,000 plus activations per year, with a blunt: penetrating injury ratios of 70%:30%, respectively. After hurricane Katrina the ratio changed in favor of more penetrating injuries with an incidence of 57%. Because of this inverse ratio, surgical intervention occurred frequently, with an increased utilization of component blood transfusion therapy. The need for better understanding of

effective early hemostatic resuscitation in patients that received massive transfusion became a necessity.

Massive transfusion defined as the transfusion of 10 or more packed red blood cell (PRBC) units in a 24-hour period carries a high mortality rates between 25% and 50%.<sup>1–5</sup> These patients can develop the “death triad” which consist of acidosis, hypothermia, and coagulopathy.<sup>6,7</sup> Current teaching is to avoid reaching these conditions by using damage control surgery.<sup>8</sup> However, conventional resuscitation practice for damage control focuses on rapid reversal of acidosis and prevention of hypothermia without taking into consideration early correction of coagulopathy. Trauma-induced coagulopathy can develop in 24.4% of patients independent of acidosis and hypothermia but secondary to trauma by itself.<sup>9,10</sup> Direct treatment of coagulopathy has been relatively neglected and viewed as a byproduct of resuscitation, hemodilution, and hypothermia.

Current management of coagulopathy-related bleeding is based on blood component replacement therapy. Recent military experience reported a high 1:1.4 plasma: RBC ratio is independently associated with improved survival primarily by decreasing death from hemorrhage. They concluded that

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massive transfusion protocols should use a 1:1 ratio of plasma to RBC for all patients who are hypocoagulable with traumatic injuries.<sup>11</sup> We hypothesize similar survival advantage when the fresh-frozen plasma (FFP):PRBC is closer to 1:1 during the first 24 hours after initial injury in a civilian trauma population requiring massive transfusion.

**PATIENTS AND METHODS**

This is a retrospective review of all adult trauma patients that required surgical intervention and arrived alive to the trauma intensive care unit, at an urban Level I Trauma Center from January 2002 to December 2006. Adult trauma patients who underwent surgical intervention with need of PRBC and FFP transfusion were included. Patients were identified through the institutional trauma registry under an IRB-approved protocol. Demographic and clinical data were retrieved from the trauma registry and charts. PRBC and FFP transfusion data were retrieved from the blood bank.

The main objective of this retrospective analysis was to analyze the impact of the FFP:PRBC ratio in the initial 24 hours on mortality. Anatomic and physiologic variables analyzed included patient age, gender, mechanism of injury, initial systolic blood pressure upon presentation to the emergency department and Injury Severity Scale score (ISS). Survival was defined as alive at discharge from the hospital. Patients who were younger than 18 years of age, who died in the emergency department, nonsurvivable head injuries, and those who did not received any FFP were excluded from the analysis.

Total amount of PRBC transfused was defined as the amount of PRBC given from initial presentation to the emergency department until the end of 24-hour period. Patients were divided into two groups; trauma patients who received

≤10 units of PRBC and those that received >10 units of PRBC during the first 24 hours of their initial injury. These were further divided into those that received a FFP to PRBC ratio of 1:1 and those that received a ratio 1:4. When the amount of PRBCs was greater than twice the number of units of FFP a ratio of 1:4 was designated. A FFP:PRBC ratio of 1:1 was assigned to patients who received <2 units of PRBCs per unit of FFP given.

Patient’s demographics, outcomes, and possible risk factors were analyzed for association by univariate analysis using Student’s *t* test and  $\chi^2$  analysis. Multiple logistic regression was applied to eliminate confounding. A standard statistical software package (SAS version 9.1, SAS Institute, Cary, NC) was used. Data are presented as numbers and standard deviations. Statistical significance was designated at the *p* < 0.05 level.

**RESULTS**

During the 4-year study period, a total of 2,746 patients with blunt and penetrating injuries underwent surgical intervention at our Level I Trauma Center. One thousand nine hundred eighty-five (72.2%) received no blood component transfusion; 626 (22.8%) received ≤10 units of PRBC; and 135 (4.9%) >10 units of PRBC. Of the 626 patients that received ≤10 units of PRBC, 250 (39.9%) received FFP, and 376 (60%) no FFP (Fig. 1).

When patient characteristics were compared between groups that received ≤10 units of PRBC and >10 units of PRBC, there was no statistical difference with regard to patient age: 31 ± SD 13 versus 33 ± SD 11 or male gender distribution: 212 (84.8%) versus 117 (86.6%), respectively. However, patients that received >10 units of PRBC had a lower systolic blood pressure upon arrival to the emergency department: 92 ± SD 27 versus 116 ± SD 15, *p* = 0.0001; a higher ISS: 27 versus 21, *p* = 0.0001; higher incidence of penetrating injuries: 97 (71.8%) versus 145 (58.0%), *p* = 0.008 and higher mortality: 75 (55.5%) versus 42 (16.8%), *p* = 0.0001 when compared with patients who received ≤10 units of PRBC (Table 1).

For patients who received ≤10 units of PRBC the average mortality was 42/250 (16.8%). When comparing FFP: PRBC ratios 1:1 versus 1:4 there was no difference between age: 29 versus 31, male gender: 84.7% versus 84.8%, incidence of penetrating injuries: 58.4% versus 57.5%, initial systolic blood pressure: 108 mm Hg versus 110 mm Hg and ISS score: 22 versus 20. However, there was a trend toward

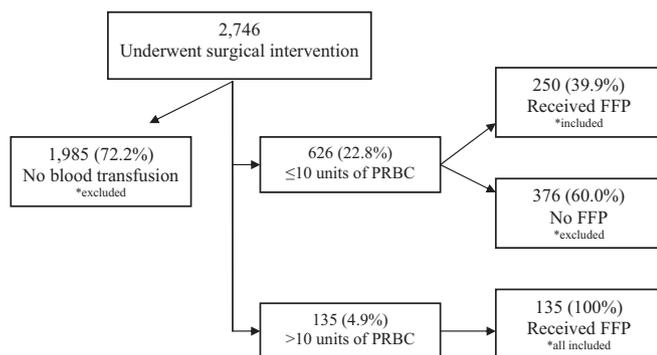


Fig. 1. Flow chart of patients included and excluded.

**Table 1 Patient Characteristics Between Transfusion Groups (≤10 Units PRBC and >10 Units PRBC)**

PRBC (n)	Age (yrs)	Gender (male)	ISS*	Mechanism† (Penetrating)	Systolic* (mm Hg)	Died*
≤10 units (250)	31 ± SD 13	212 (84.8%)	21	145 (58.0%)	116 ± SD15	42 (16.8%)
>10 units (135)	33 ± SD 11	117 (86.6%)	27	97 (71.8%)	92 ± SD27	75 (55.5%)

\* *p* = 0.001.

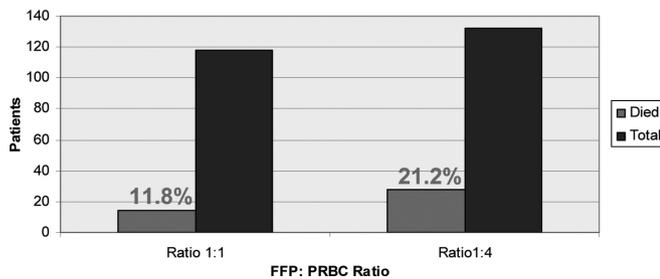
† *p* = 0.008.

ISS, Injury Severity Scale score; PRBC, packed red blood cells.

**Table 2** Univariate Analysis FFP:PRBC Ratio in Patients With ≤10 Units PRBC

	FFP:PRBC Ratio 1:1	FFP:PRBC Ratio 1:4
Patients, n = 250	118	132
Age (yrs) (years)	29	31
Gender (% male)	100 (84.7)	112 (84.8)
Mechanism (% penetrating)	69 (58.4)	76 (57.5)
Systolic Pressure (mm Hg)	108	110
ISS	22	20
Died (%)	14 (11.8)	28 (21.2)

$p > 0.05$ .



**Fig. 2.** Mortality in patients with ≤10 units PRBC stratified by FFP:PRBC ratio.

increased mortality in patients that received a FFP:PRBC ratio of 1:4, 14 (11.8%) versus 28 (21.2%),  $p = 0.06$  (Table 2, Fig. 2).

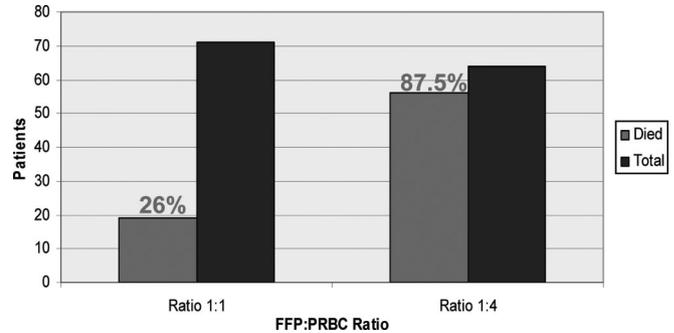
In patients who received >10 units of PRBC, 75 of 135 (55.5%) died. When stratifying for FFP: PRBC ratio's 1:1 versus 1:4 there was no difference in age, male gender, incidence of penetrating injuries, initial systolic pressure and ISS. A significant difference in mortality was noted in patients with FFP:PRBC ratio of 1:4, 56 of 64 (87.5%) versus 19 of 71 (26%),  $p = 0.0001$ . Patients in the 1:1 group died from ongoing bleeding 3 of 19 (15.7%) early after ICU admission within the first day and 16 of 19 (84.2%) died of multiple organ failure at day  $18 \pm SD 12$ . In the 1:4 group patients died from ongoing bleeding 11 of 56 (19.6%) early after ICU

**Table 3** Univariate Analysis FFP:PRBC Ratio in Patients With >10 Units PRBC

	FFP:PRBC Ratio 1:1	FFP:PRBC Ratio 1:4
Patients (n = 135)	71	64
Age (yrs)	27	33
Gender (% male)	63 (88.7)	54 (84.3)
Mechanism (% penetrating)	53 (74.6)	44 (68.7)
Systolic Pressure (mm Hg)	95	91
ISS	25	29
Died (%)*	19 (26)	56 (87.5)

\*  $p = 0.0001$

FFP, fresh frozen plasma; ISS, Injury Severity Scale score; PRBC, packed red blood cells.



**Fig. 3.** Mortality in patients with >10 units PRBC stratified by FFP:PRBC ratio.

**Table 4** Multiple Logistic Regression for Mortality Risk in Patients With >10 Units PRBC

Variables	$p$	Odds Ratio (95% CI)
Ratio*	0.001*	18.88 (6.32–56.36)*
ISS	0.23	1.02 (0.99–1.06)
Systolic	0.43	0.99 (0.98–1.01)
Mechanism	0.60	1.34 (0.43–4.17)
Sex	0.57	1.64 (0.29–9.17)

ISS, Injury Severity Scale score; PRBC, packed red blood cells.

admission and 45 of 56 (80.3%) died of multiple organ failure at day  $16 \pm SD 8$  (Table 3, Fig. 3).

Using multiple logistic regression in the group of patients who received >10 units of PRBC, a difference in ratio 1:1 versus 1:4 was the only variable that was consistent with increased risk of mortality (relative risk, 18.88; 95% CI, 6.32–56.36,  $p = 0.001$ ) (Table 4).

## DISCUSSION

Although overall survival in massive transfusion for trauma patients has risen from roughly 6% to above 50%,<sup>12</sup> bleeding is still the cause of death in up to 40% of trauma victims.<sup>13</sup> In trauma patients, with evidence of uncontrolled hemorrhage, the development of hypovolemic shock, hypothermia, and coagulopathy occurs frequently. When trauma induced coagulopathy is already present, treatment can be very difficult with subsequent increase in mortality.<sup>9</sup> As such, trauma induced coagulopathy remains an important clinical problem.

Transfusion of whole blood has been largely abandoned by the civilian medical community because of the availability of component therapy. Yet, some military experience suggests that there is still a place for fresh whole blood, especially where massive transfusion is required. Indeed, in the setting of massive transfusion, whole blood may even be preferable to component therapy for hemostatic resuscitation, but studies on trauma patients requiring massive transfusion are limited and inconclusive.<sup>14–17</sup>

The advent of whole blood fractionation techniques in the decades after WWII allowed efficiency through the use of

PRBCs, FFP, platelet concentrates, and cryoprecipitate,<sup>18,19</sup> while simultaneously limiting risk of infection and transfusion reaction.<sup>20</sup> Yet, this transition may have limited clotting factor replacement in trauma patients requiring massive transfusion. Component therapy became the standard of care through the 1970s without undergoing any rigorous comparison to whole blood therapy in the treatment of trauma. Some studies comparing whole blood versus component therapy have been performed, but they are small and in elective surgical populations.<sup>21–24</sup>

The main objective of our study was to demonstrate in a civilian trauma setting that patients requiring massive transfusion, have better outcomes when the ratio of blood transfusion to FFP (FFP:PRBC) is closer to 1:1 as opposed to 1:4. Our results and recent military experience suggest that those patients that required massive transfusion may have a survival benefit when the ratio of FFP:PRBC was closer to 1:1 during the first 24 hours after initial injury.

In our study, 27.7% of the patients required blood component therapy of some kind. When patients that received  $\leq 10$  units of PRBC were compared with those that received  $>10$  units of PRBC a statistical difference in physiologic and anatomic variables were evident. Patients who received  $>10$  units of PRBC transfusion had, as expected, a lower initial systolic blood pressure upon arrival to the emergency department, higher ISS, higher incidence of penetrating injuries and increased mortality, and were clearly more seriously injured.

Although the main objective of our study was to look specifically those injured patients with requirements of  $>10$  units PRBC, a comparison of those patients that received  $\leq 10$  units of PRBC was included to demonstrate any potential trends toward increase in mortality. In this subset of patients, no difference in patient physiologic and anatomic characteristics was demonstrated. When the 1:1 versus 1:4 ratio was compared, a trend toward increased mortality 14 (11.8%) versus 28 (21.2%),  $p = 0.06$  was noted.

Recent studies report that most patients with severe injuries are coagulopathic at arrival to the emergency department even before aggressive resuscitation interventions.<sup>9,25,26</sup> Some studies suggest that along with aggressive surgical hemostasis, prompt early correction of coagulopathy with early utilization of plasma may be effective in decreasing PRBC requirement with subsequent improvement in outcome.<sup>27,28</sup>

Benefits of early use of plasma have also been demonstrated in an experimental pharmacokinetic model. Once excessive deficiency of factors has developed, 1 to 1.5 units of FFP must be given for every unit of PRBC transfused to correct the deficit. When FFP transfusion is started before plasma factor concentration drops below 50% of normal, an FFP:PRBC transfusion ratio of only 1:1 corrects coagulopathy.<sup>29</sup>

Although traditionally attributed to hemodilution, acidosis, and hypothermia, recent studies indicate that coagulopathy starts very soon after trauma with incidence of 24% to

28% upon presentation to the emergency department. This coagulopathy can exacerbate bleeding in 25% to 50% of trauma patients and has been shown to correlate with increased mortality.<sup>9,30,31</sup>

Direct treatment of trauma-induced coagulopathy has been relatively neglected and viewed as a byproduct of resuscitation, hemodilution, and hypothermia. A close FFP to PRBC ratio in combination with damage control surgery, addresses the entire lethal triad immediately upon admission.<sup>10</sup> By demonstrating that in the severely injured the coagulopathy of trauma is present at admission, recent studies have brought back to light the importance of treating this disorder at an earlier stage.<sup>9,32,33</sup>

In the group of patients who received  $>10$  units of PRBC with 1:4 versus 1:1 ratio, a 62% increased mortality was demonstrated. In other words, early hemostatic resuscitation with 1:1 FFP to PRBC ratio conveys a survival benefit for patients in need of massive blood transfusion as demonstrated in our multiple logistic regression analysis. Results by Cosgriff et al.,<sup>34</sup> in severely injured patients with mean ISS  $>30$  who received  $>10$  units PRBC in the first 24 hospital hours after injury, had a documented increase incidence of severe coagulopathy (47%) in the OR with elevation of PT and PTT above normal, which further supports the need for early hemostatic resuscitation.

Early institution of hemostatic resuscitation with a 1:1 FFP to PRBC ratio can be accomplished through massive transfusion protocols (MTP). It has been demonstrated in several studies that implementation of such protocols, facilitates the process of obtaining blood components in an efficient and expeditious fashion.<sup>35</sup> At our institution, our current MTP gets activated by the trauma surgeon from the emergency department or during surgical intervention with immediate preparation of 6 units of PRBC, 6 FFP, 6 platelets, and 10 of cryoprecipitate. We feel that implementation of early hemostatic resuscitation thru our MTP has helped us achieve better outcomes.

## CONCLUSION

This study compares ratios of FFP:PRBC given in a civilian trauma center to patients who required blood component therapy of  $\leq$  and  $>10$  units of PRBC. There is a survival benefit in patients requiring massive transfusion when the FFP:PRBC ratio is closer to 1:1, rather than 1:4. The development of an MTP that will target early institution of hemostatic resuscitation through a 1:1 FFP to PRBC ratio will decrease mortality in this subset of trauma patients. A randomized prospective study is needed to confirm this retrospective review.

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## DISCUSSION

**Dr. Peter Rhee** (Tucson, Arizona): It is finally being recognized that blood is immensely complex and was designed by an ingenious creator, whoever she may be.

Stolen cars are stripped and sold as parts as one can make more money that way and this is also true for blood. The idea of component therapy has sufficed for most medical and surgical scenarios.

However, in trauma when many blood volumes are sometimes lost and replaced, the body may not tolerate the component approach for many complex reasons. Sometimes, component therapy is like eating the coffee beans, then the sugar, then the cream, then the hot water and then gyrating to make coffee inside your body.

Currently, observations from the current war have been that early and aggressive use of blood products and in particular whole blood seems to be beneficial. Many US Military surgeons have been adopting the idea of “Haemostatic Resuscitation” which entails the utmost priority on hemorrhage control, utilization of permissive hypotension, minimization of crystalloid use, early use of hypertonic saline, early use of PRBC until fresh whole blood is available, and the use of local and systemic hemostatics. The adoption of this practice may be one of the variables that have resulted in the best outcome in the history of Military Medicine.

Dr. Duchesne and co-authors were inspired by the reports of aggressive fresh frozen plasma use and have attempted to validate the results using a civilian database. They have in brief shown that the patients who received more FFP survive more often than those who do not. Therefore, their conclusion was that more FFP is better and less is not.

The study confirms my personal bias but there are some significant issues with this study that should be considered by

the audience. This is a small study from only one institution. There were only 135 patients that received more than 10 units of blood.

This emphasizes that only 5% of patients requiring surgical intervention receive more than 10 units of blood and that big time bleeders are uncommon. Thus the recommendation of aggressive FFP use may only apply to a small population of patients.

The first question that I have is whether the authors looked at other products such as platelet, cryoprecipitate and factor 7 use as they may also play an important role and they are associated with increased FFP use. Is it possible that these types of products are the responsible variable and not FFP?

Second question: did you have an opportunity to look at this data at various intervals rather than 1:2? The cut off point in this study for which group the patients fell into was whether they received more or less than a ratio of 1:2.

Thus the terminology of 1:1 and 1:4 used in this study is not true and is misleading. When we looked at the data from Los Angeles, we found similar results and the survival rate for 1:4 was poor but equivalent for 1:2 compared to 1:1.

The third question: did you examine this trend in patients not requiring surgery? This may tell us more about the cessation of hemorrhage due to FFP.

I often find that in patients requiring surgical intervention, one major factor for death is the ability to gain surgical control of hemorrhage and possibly the condition of suture-emia.

Fourth and last question: did you look at the trends over time? In Los Angeles, we have found that there has been significant change in FFP use over time with concomitant decrease in PRBC use.

I would like to thank the authors for providing the manuscript in a timely manner and the members of the AAST for the opportunity to discuss this important paper.

**Dr. Juan A. Asensio** (Miami, Florida): That was a very intriguing paper. This and some of the other papers at this meeting have once again raised new questions with regard to component therapy.

In our study of 548 patients that exsanguinated and underwent damage control, we looked at fresh frozen plasma and it did not seem to be a single independent predictor of outcome, rather the transfusion of greater than 10 to 14 units of blood or at least one whole blood volume was the single strongest independent predictor of outcome (Asensio JA, McDuffie, Petrone P, Roldan G, et al: Reliable Variables in the Exsanguinated Patient which Indicate Damage Control and Predict Outcome. *Am J Surg* 2001;182:743–751).

My question to you is could your mortality be related, also, to the amount of red blood cells that you transfused? And how many of these patients underwent damage control?

I think this study is very provocative and it is opening once again the opportunity to revisit something that may have been considered a “sacred cow” that might yet still need to be slain.

**Dr. John B. Holcomb** (San Antonio, Texas): I would just like to echo some of the previous comments and ask a couple of questions. First, these studies are difficult to do, especially at a single site largely because of the small numbers of patients who actually receive a massive transfusion, only about 2% of admissions at a civilian trauma center actually receive a massive transfusion. However, these are the patients who are potentially salvageable yet go on to die so they're extremely important to study.

I would congratulate you for including the plasma:RBC range effect. If you shoot for 1:2 you're going to end up on the left-hand side at one to three to one to four half the time. Mortality is clearly higher in that range by giving less plasma.

My bias is to strive for 1:1, knowing that you'll occasionally slip to 1:2, but avoid the 1:3, so I think your group is exactly right.

I would just like to ask you a couple of questions. Just like Dr. Kashuk highlighted the other day, was there a difference at six hours? We've seen that over and over and over in four papers at this meeting dealing with this area. Six hours seems to be important.

I'd like you to explore a little bit the blunt-penetrating rates and see if there is a difference in outcome related to mechanism of injury and plasma:RBC ratio. There maybe different types of bleeding and rates of bleeding with those different mechanisms.

And then, importantly, I think you should present data about cause of death, when they died, where they died—on the OR table or on the ICU, these three data points are important to present because you don't want to give the impression that 100% of your patients died of TRALI by giving more FFP. You need to show that death was or was not caused by TRALI, hemorrhage, sepsis or head injury, and how those causes changed based on ratios of plasma. This important concept is outlined in the paper by Borgman et. al (*J Trauma*, Oct 07). Thank you very much for your important paper.

**Dr. Jeffrey L. Kashuk** (Denver, Colorado): I rise to compliment you on an important review of massive transfusion practices from New Orleans. I'd like to first point out, as our group emphasized yesterday, that the “ballgame” is over after 6 hours in this group. In our experience, over 80% of transfusions were completed during this time period. Furthermore, this point was re-enforced by your data showing little changes in the mortality rates in patients receiving less than 10 units of blood compared to those with greater amounts transfused. Therefore, I agree with Col. Holcomb that it's important to re-evaluated your data in terms of the six hour transfusion threshold.

Secondly, I would take issue with your conclusion of endorsing 1:1 FFP:RBC, as you stated clearly in your presentation that your survival threshold was closer to 1:2. This is misleading. I believe we must try to be more specific in our definitions as we all struggle to ascertain whether 1:1 is the ideal in the civilian population.

Finally, I believe that the multi-center trial will certainly be essential to help answer some of these questions.

**Dr. Steven R. Shackford** (Burlington, Vermont): This would only make sense to me if you could tell us how many patients in each group truly died of exsanguination. I think that's what John was kind of coming up to.

How many patients in the one to one, in the one to four really died of exsanguination? Because a lot of those deaths may have been head injury and everything else and they're confounders. I think it's important to know that.

**Dr. Juan C. Duchesne** (New Orleans, Louisiana): The first question regarding the incorporation of cryoprecipitate and platelets in our study, although this was not evident in our retrospective study, we are currently working on implementing early hemostatic resuscitation in our massive transfusion protocol.

And with this we will be able to study prospectively these variables. Unfortunately, because of the retrospective nature of this study, basically we did not include these variables but think they can be included in a prospective evaluation.

In regards to the second question I have here is in regards to ratio. Just because we actually decided for our study to, we defined our ratio of one to one as basically the amount of packed red cells that was less than two units per unit of FFP.

This was our decision on the rationale of what we were going to study. Again, this is a retrospective analysis. And if you basically looked into which patient had a perfect one to one ratio I will be very surprised to get a bunch of numbers to a retrospective analysis.

In regards of Question Number 3, just surgical patients were included. I don't remember exactly the question but I just put here that the patients that were included were just surgical patients. We did not look at patients that did not undergo surgical procedures.

In regards to the difference in trends per year, because of the nature of the study, again, and lack of protocols for transfusion ratio there was no obvious trends noticed per year in regards to mortality.

I am going to try to answer the rest of the questions. Dr. Asensio, thank you for your comments. We noticed that actually, yes, in the patients that we received more than 10 units RBC was actually independent risk factor for increasing mortality.

Dr. Holcomb, there was definitely an increase in the incidence of penetrating mechanism for the patients that received more than ten units of packed red blood cells.

More need of packed red blood cells was actually utilized in this group of patients and they actually reached a significant difference.

And when they died in the operating room, that's an excellent question. And actually the vast majority were able to get to the SICU. The exact number, I don't have it with me but we would be more than happy to look into that and put it in our paper.

In regards of 6 hours versus 24 hours, the main reason why we decided to do 24 hours is because we were trying to simulate the same study that Dr. Holcomb will be hopefully publishing in the *Journal of Trauma* next month.