Original Article

Futility Assessment of Recombinant Factor VII Activated for the Treatment of Hemorrhagic Shock Requiring Massive Transfusion

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Abstract

Objective: Recombinant human factor VII activated (rFVIIa) is an adjuvant therapy in patients receiving massive transfusion for hemorrhagic shock. We compared patient characteristics and outcomes to determine futility criteria for the administration of rFVIIa in patients receiving massive transfusion for hemorrhagic shock.

Methods: This was a retrospective cohort analysis of patients who received both massive transfusion and rFVIIa. Consecutive trauma patients were allocated to 1 of 2 cohorts: survivors and nonsurvivors.

Results: Seventy-two subjects comprised the study: 27 were survivors and 45 were nonsurvivors. A univariate analysis revealed that nonsurvivors were older and had a more profound coagulopathy as measured by prothrombin time. A stepwise logistic regression revealed an increased odds of death in those patients who were older (odds ratio [OR], 1.048; 95% CI, 1.008-1.091), had a higher admission prothrombin time (OR, 1.561; 95% CI, 1.152-2.116), and received more fresh frozen plasma (OR, 1.098; 95% CI 1.023-1.179). In addition we saw a protective effect with increased platelet administration (OR, 0.645; 95% CI, 0.446-0.932).

Conclusion: The use of rFVIIa for massive transfusion in middle-aged patients with moderate coagulopathy experiencing hemorrhagic shock may be considered futile. However, if rFVIIa is to be used as part of a massive transfusion protocol, adequate administration of platelets should be ensured.

Key Words—blood transfusion, coagulopathy, factor VIIa, futility, multiple trauma, plasma, platelets

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Hemorrhage is a significant contributor to mortality in the surgical intensive care unit and is a leading cause of death in the trauma population.¹ In this patient population, excessive hemorrhage leads to coagulopathy caused by hemodilution, consumption of coagulation factors, fibrinolysis, and hypothermia.² Massive transfusion is often initiated along with fresh frozen plasma (FFP), platelets, and cryoprecipitate in an attempt to alleviate this coagulopathy. Those patients who require a massive transfusion, defined as receiving 10 units of packed red blood cells (pRBC) in a 24-hour period,

have a much greater risk of death as compared to patients who receive less blood.³ One study showed a mortality rate of 22% in patients who received 1 to 10 units of pRBC compared to 30% in those who received 11 to 20 units, 50% in those who received 21 to 40 units, and 59% in those who received more than 40 units ($P < .001$).⁴

Trials evaluating the use of recombinant human factor VII activated (rFVIIa) in patients with blunt and penetrating trauma have shown a modest but statistically significant decrease in the number of required pRBC.⁵⁻⁸ However, other trials have shown an

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increased risk of thromboembolic complications with rFVIIa use.⁵⁻⁷ Due to the possibility of an increased risk of thromboembolic complications, the increased cost associated with rFVIIa, and failure of any data to demonstrate improved mortality, careful evaluation should be given to appropriate patient selection. Based on the results of a previous futility study (evaluation of patient characteristics that might predict unsuccessful use of rFVIIa), acidosis, coagulopathy, and a low Revised Trauma Score (RTS) have been associated with a poor response to rFVIIa administration.⁹ Notably, the study included all patients with acute hemorrhagic shock. It did not specifically take into account those patients who required massive transfusion. As noted in our discussion, a more thorough evaluation of patients requiring rapid administration of blood was warranted. Therefore, the purpose of our study was to evaluate futility criteria for the administration of rFVIIa in patients who require massive transfusion for the treatment of hemorrhagic shock.

METHODS

A retrospective cohort analysis was conducted at a Level 1 trauma center with a 32-bed surgical intensive care unit. The study was reviewed and approved by the local institutional review board. Patients admitted to the surgical intensive care unit from March 1, 2007, to October 12, 2011, were screened for enrollment via the institution's trauma registry and pharmacy database. To be eligible, the patient had to be at least 15 years of age and receive both massive transfusion and rFVIIa. Massive transfusion was defined as replacement of a patient's entire blood volume within a 24-hour period (10-12 units of pRBC), a need for at least 4 units of pRBC within 4 hours with continued major bleeding, or a blood loss exceeding 150 mL/min. At the study site, the attending trauma surgeon, attending critical care physician, or attending anesthesia physician made the determination to institute the massive transfusion protocol. This protocol required obtaining hemoglobin and hematocrit levels, as well as a prothrombin time and international normalized ratio (INR) before transfusion of the first blood pack. These tests were also performed after the transfusion of each blood pack. Blood packs consisted of 4 units of pRBC, 4 units of FFP, and a 6-pack of platelets. Blood packs were automatically provided by the blood bank every 15 to 30 minutes until the protocol was canceled. Patients were transfused with type-specific or cross-matched blood whenever possible. If unable to provide type-specific blood, females

under the age of 50 years were given O-negative blood. All others received O-positive blood. After the third blood pack was transfused, rFVIIa 90 to 100 mcg/kg and cryoprecipitate were considered but not required by the massive transfusion protocol.

Once screened and found eligible, patients were placed into 1 of 2 cohorts. Cohort 1 consisted of patients who received both massive transfusion and rFVIIa and survived (survivors). Cohort 2 consisted of patients who received both massive transfusion and rFVIIa and died (nonsurvivors).

The following demographic and laboratory values were recorded for each patient: sex, admitting trauma (blunt or penetrating), age, Injury Severity Score (ISS), RTS, admission temperature, admission prothrombin time (PT), admission INR, admission pH, admission base deficit, number of units of pRBC received in the first 24 hours of admission, total number of units of pRBC received, and total number of units of FFP, platelets, and cryoprecipitate received.

The chi-square test, Student *t* test, and Mann-Whitney *U* test were used for univariate analysis of nominal, continuous, ordinal data and continuous data that are not normally distributed. Differences between the 2 cohorts were considered statistically significant with an a priori $\alpha = 0.05$. In addition, a stepwise logistic regression was performed. Statistical analysis was performed with SPSS 16.0 (SPSS, Inc., Chicago, IL).

RESULTS

During the period from March 1, 2007, to October 12, 2011, 72 patients at least 15 years old received both massive transfusion and rFVIIa for hemorrhagic shock. Twenty-seven survived the event and were allocated to the survivors group and the other 45 died during the event and were consequently allocated to the nonsurvivors group. Among all participants, the overall mortality rate was 62.5% and the average amount of pRBC received in the first 24 hours was 27.6 ± 21.3 units.

However, when comparing the 2 cohorts using a univariate model (Table 1), we saw that nonsurvivors tended to be older (32.5 ± 14.3 vs 44.4 ± 19.3 ; $P = .005$), have a longer PT (12.3 ± 3.1 vs 16.4 ± 9.8 ; $P = .008$), and have a higher INR (1.2 ± 0.2 vs 1.6 ± 1.0 ; $P = .039$) at massive transfusion protocol initiation. All other variables were found to be similar between the groups.

To assess the effect of baseline variables on the odds of mortality, a stepwise logistic regression was performed. All baseline demographic and laboratory

Table 1. Characteristics of cohort 1 versus cohort 2

Variable	Survivors (n = 27)	Nonsurvivors (n = 45)	P value
Male sex ^a	17 (63)	35 (78)	.174
Age, years ^c	32.5 ± 14.3	44.4 ± 19.3	.005
Blunt trauma ^a	17 (63)	37 (82)	.068
Injury Severity Score ^b	34.1 ± 17.6	33.0 ± 16.7	.800
Revised Trauma Score ^b	7.2 ± 4.0	7.1 ± 3.9	.938
Body temperature, °C ^c	35.8 ± 0.5	35.9 ± 0.8	.860
Prothrombin time, seconds ^c	12.3 ± 3.1	16.4 ± 9.8	.008
INR ^c	1.2 ± 0.2	1.6 ± 1.0	.039
pH ^b	7.2 ± 0.1	7.1 ± 0.2	.062
Base deficit, mMol/L ^b	10.4 ± 5.8	11.7 ± 6.5	.379
Red blood cells in first 24 hours, units ^c	23.5 ± 14.9	30.1 ± 24.2	.466
Total red blood cells, units ^c	31.2 ± 18.7	32.6 ± 23.7	.731
Fresh frozen plasma, units ^b	20.9 ± 15.8	21.6 ± 16.3	.845
Platelets, units ^b	4.5 ± 3.8	3.4 ± 2.9	.168
Cryoprecipitate, units ^c	0.81 ± 1.2	0.4 ± 0.9	.088

Note: Data intervals refer to mean ± SD. Other data refer to number (%) of patients. All laboratory values were measured at admission. INR = international normalized ratio.

^aChi-square test

^bStudent *t* test.

^cMann-Whitney *U* test.

parameters were included in the initial model. The final significance model ($r^2 = 0.55$) found increased odds of death in patients with increased age (OR, 1.048; 95% CI, 1.008-1.091; $P = .020$), increased PT (OR, 1.561; 95% CI, 1.152-2.116; $P = .004$), and increased FFP administration (OR, 1.098; 95% CI, 1.023-1.179; $P = .010$). Also, a protective effect for administration of platelets (OR, 0.645; 95% CI, 0.446-0.932; $P = .019$) was observed.

DISCUSSION

The results of our study suggest that each increase in year of life is associated with a 4.8% increased odds of death (holding all other variables constant), suggesting that use of rFVIIa even in middle-aged patients who are receiving massive transfusion may be futile. Also, our model revealed increased odds for death by 9.8% and 56.1% for each increase in unit of FFP administered and each second increase in PT, respectively. This suggests that the use of rFVIIa in patients presenting with moderate coagulopathy may be futile as well. However, we did find that those patients who received more platelets may have had reduced odds of death by 1.9%. Though it did not reach statistical significance, a large difference was observed between survivors and nonsurvivors re-

garding the amount of cryoprecipitate administered. Those patients who survived received twice as much cryoprecipitate as those who died (0.81 ± 1.21 vs 0.4 ± 0.86 ; $P = .088$).

In the study conducted by Stein and colleagues, serum lactate, PT, and RTS were found to be significant independent predictors of response to rFVIIa in patients with coagulopathy secondary to acute hemorrhagic shock.¹⁰ However, in our study, we were unable to evaluate serum lactate due to the lack of available data for the included subjects. We were able to evaluate PT and RTS and found that an elevated PT is associated with increased odds of death. In addition, our larger study was able to show that increased age was a predictor of futility. In the logistic regression conducted by Stein and colleagues, age approached statistical difference (OR, 1.020; 95% CI, 0.981-1.061), suggesting that more observations may have made this variable a predictor of futility. As compared to the study by Stein and colleagues, our sample received more pRBC (27.6 ± 21.3 vs 25 ± 13) and had a shorter PT (15.1 ± 8.1 vs 17.68 ± 5.53). In fact, when we compare patients who did not respond to rFVIIa, the disparity in prothrombin time is even more apparent between the 2 studies (16.4 ± 9.8 vs 21 ± 6.5). These findings, in addition to difference in

rFVIIa dosing regimens (50 to 100 mcg/kg vs 90 to 100 mcg/kg), may account for our study being unable to replicate some of the previously reported findings and discovering new predictors for rFVIIa futility in patients requiring massive transfusion.

Though our findings suggest that the use of rFVIIa as adjunct treatment in patients at the upper limit of the included age range and those presenting with moderate coagulopathy would be futile, our study is not without limitations. As noted in a previous study collecting similar data, there is significant collinearity among the variables analyzed.⁹ Thus, it is difficult to determine the true source of the differences observed between our groups.

In addition, our study sample received a very large volume of blood in a 24-hour period. Due to the retrospective nature of this trial, it is difficult to determine at what point the decision to administer rFVIIa was made or the total dose of rFVIIa administered. Because of the large number of pRBC administered, the use of rFVIIa may have represented a final effort to reduce the risk of exsanguination. Based on this, rFVIIa may have been utilized only in the very ill, which would lead to a significant selection bias in our trial. The addition of timing as well as the total dose of rFVIIa may have added to the results of our study. In the trial by Clark et al, the “last-ditch” use of rFVIIa was shown to be ineffective. In that retrospective study, the outcome of 50 patients treated with massive transfusion and rFVIIa was assessed. Severe coagulopathy was defined as an activated partial thromboplastin time greater than 1.5 times the normal range, a platelet count of less than $50 \times 10^9/L$, and a fibrinogen level of less than 1 g/L or a thrombin time greater than 1.5 times the normal level. Seventy percent of the patients who received rFVIIa had a severe coagulopathy as compared to an overall rate of 42%. The investigators found that severe coagulopathy was associated with higher mortality at 7 days (52% vs 21%; $P = .02$). The authors concluded that the administration of rFVIIa to patients with severe coagulopathy did not significantly alter outcomes.¹¹

The paucity of randomized prospective trials evaluating the efficacy of rFVIIa in the trauma population, and specifically in those patients requiring massive transfusion for hemorrhagic shock, makes determining appropriate criteria for rFVIIa use difficult. The impact on mortality of rFVIIa used as an adjunct treatment in patients in hemorrhagic shock requiring massive transfusion is inconclusive.

CONCLUSION

The adjunctive use of rFVIIa in middle-aged patients and those with moderate coagulopathy who are experiencing hemorrhagic shock requiring massive transfusion may be considered futile. However, if rFVIIa is to be used as part of a massive transfusion protocol, adequate administration of platelets should be ensured.

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