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Factor VIIa administration in traumatic brain injury: an AAST-MITC propensity score analysis

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ABSTRACT

Background Recombinant factor VIIa (rFVIIa) has been used off-label as an adjunct in the reversal of warfarin therapy and management of hemorrhage after trauma. Only a handful of these reports are rigorous studies, from which results regarding safety and effectiveness have been mixed. There remains no clear consensus as to the role of rFVIIa in traumatic brain injury (TBI).

Methods Eleven level 1 trauma centers provided clinical data and head CT scans of patients with a Glasgow Coma Scale (GCS) score of ≤13 and radiographic evidence of TBI. A propensity score (PS) to receive rFVIIa in those surviving ≥2 days was calculated for each patient based on patient demographics, comorbidities, physiology, Injury Severity Score, admission GCS score, and treatment center. Patients receiving rFVIIa within 24 hours of admission were matched to patients who did not receive rFVIIa for outcomes assessment. Subgroup analysis evaluated patients with primary head injury with PS matching.

Results There were 4284 patient observations; 129 received rFVIIa. Groups were comparable after matching. No differences in mortality or morbidity were found. Improvement in GCS score from admission to discharge was less among those receiving rFVIIa (5.5 vs. 2.4; P value 0.001); however, there was no difference in average GCS score at discharge. No significant differences in outcomes were identified in patients with isolated TBI receiving rFVIIa.

Discussion rFVIIa in early management of TBI is not associated with a decreased risk of mortality or morbidity, and may negatively impact recovery and functional status at discharge in the severely injured patient with polytrauma.

Level of evidence Level III.

Study type Therapeutic/care management.

BACKGROUND

Traumatic brain injury (TBI) and hemorrhage are the first and second most common causes of death, respectively, in the setting of trauma.[1] Despite injury prevention efforts, TBI-related emergency room visits have increased over the past decade, with falls accounting for 40% of all TBIs.[2] Although advances in supportive care have contributed to decreased TBI mortality, fall-related deaths are on the rise, with the majority occurring among patients aged 65 years and over.[3-5]

The pathophysiology of polytrauma is such that post-traumatic stressors and complications (eg, infections, reperfusion injury, operative interventions, and so on) induce a second insult that further augments the initial inflammatory response, increasing the risk of multiple organ dysfunction syndrome (MODS). Likewise, severe TBI has been associated with increased activation of various inflammatory mediators, which in turn leads to consumption of existing coagulation factors and activation of anticoagulation pathways.[6] In the setting of polytrauma, this resulting TBI coagulopathy can contribute to ongoing acute hemorrhage both within the brain and at other sites, thereby increasing blood product requirements necessary for adequate resuscitation.

Recombinant factor VIIa (rFVIIa) in the setting of trauma is an attractive treatment option given that replacement of depleted endogenous factor VII (FVII) may slow bleeding in the setting of TBI coagulopathy. Among the general trauma population, rFVIIa was not associated with improvement in survival, but had a small positive effect on transfusion requirements and rates of adult respiratory distress syndrome (ARDS).[7 8] As such, support for the continued use of rFVIIa in the trauma setting stems from studies showing its efficacy in patients on anticoagulation. Although rFVIIa can effectively and rapidly normalize traditional (eg, international normalized ratio (INR), partial prothromboplastin time (PTT) and emerging (eg, thromboelastography (TEG)) parameters used to characterize the coagulopathic state for patients on anticoagulants, some studies have failed to show a clinical benefit.[9-11] Data supporting rFVIIa use in the setting of TBI are less convincing and limited by the marginal quality of available prospective reports.[11-13] Although there are several studies evaluating the evolution of intracranial hemorrhage (ICH) after rFVIIa administration, there has been no formal evaluation of functional outcomes of patients with TBI receiving rFVIIa.[9 10 14]

The known characteristics of rFVIIa—the rapid correction of coagulation parameters, low infusion volume, and reasonable safety profile—make it an attractive hemostatic adjunct for correction of coagulopathy particularly in patients with TBI with limited physiologic ability to tolerate large volume resuscitations. We therefore sought to determine if its use in a large group of patients with TBI was associated with improved outcomes through a propensity score analysis.

METHODS
Data acquisition

Retrospective data of patients with TBI were acquired from 11 level 1 US trauma centers from 2008 to 2009, as described previously.[15] Inclusion criteria included age 16 years or older, evidence of

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Table 1 Cohort demographics, prematching and postmatching

	Prematching			Postmatching, all comers			Postmatching, primary TBI		
	−FVII (n=3366)	+FVII (n=95)	P value	−FVII (n=96)	+FVII (n=49)	P value	−FVII (n=37)	+FVII (n=20)	P value
Age	41 (21)	49 (23)	<0.001	52 (23)	50 (22)	0.570	57 (23)	59 (21)	0.675
Male	75.4%	61.0%	0.001	56.3%	57.1%	0.918	56.8%	60.0%	0.813
BMI	25.9 (6.3)	26.7 (6.4)	0.269	25.7 (6.8)	26.9 (5.9)	0.291	26.7 (7.8)	27.2 (6.5)	0.813
Smoker	7.4%	2.1%	0.049	6.3%	0%	0.074	5.4%	0%	0.290
Warfarin	2.0%	17.9%	<0.001	9.4%	14.3%	0.372	13.5%	25.0%	0.277
Comorbidity	12.5%	23.2%	0.002	26.0%	30.6%	0.560	35.1%	35.0%	0.992
Previous MI	1.7%	4.2%	0.071	4.2%	4.1%	0.981	2.7%	0%	0.458
Prior stroke	1.8%	5.3%	0.014	9.4%	6.1%	0.501	5.4%	10.0%	0.517
CHF	1.1%	2.1%	0.339	4.2%	2.0%	0.507	2.7%	0%	0.458
COPD	1.2%	1.1%	0.904	0%	0%	1.000	5.4%	0%	0.290
Diabetes	6.6%	9.5%	0.268	4.2%	10.2%	0.154	13.5%	20.0%	0.522
Dialysis	0.6%	3.2%	0.002	1.0%	4.1%	0.224	0%	5.0%	0.170
Liver disease	1.7%	4.2%	0.061	8.3%	6.1%	0.634	5.4%	5.0%	0.948
Malignancy	1.9%	2.1%	0.869	5.2%	4.1%	0.765	8.1%	0%	0.191

BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; FVII, recombinant factor VIIa; MI, myocardial infarction; TBI, traumatic brain injury.

blunt TBI on admission head CT, and admission Glasgow Coma Scale (GCS) score of 13 or less. Patient demographics (age, gender, smoking), coagulation status (±warfarin), pre-existing comorbidities, and actual admission CT scans were collected using an online web-portal data entry system developed in conjunction with the American Association for the Surgery of Trauma and Acute Care Surgery. CT scans were reviewed by the primary research site and graded according to the Marshall classification scheme.[16] Comorbidities were considered both individually and as a composite dichotomous variable representing the presence of any known pre-existing medical condition at the time of admission (table 1). Trauma mechanism (blunt vs. penetrating), admission physiology, labs, degree of coagulopathy, and initial resuscitation requirements were also collected.

Outcomes
The primary outcome of interest was inhospital mortality. Deaths occurring within the first 24 hours of admission were excluded from all further analyses. The secondary outcomes consisted of morbidities commonly occurring among patients with trauma admitted to intensive care units (ICUs) and with prolonged hospitalizations (ventilator-associated pneumonia, ARDS, deep venous thrombosis (DVT), catheter-related blood stream infection, abscess, or meningitis), as well as functional status at discharge (GCS score at discharge, discharge disposition). Discharge disposition was treated as a dichotomous variable, with surviving patients being discharged to either a private residence versus a rehabilitation facility, a long-term assisted care, or skilled nursing facility. These categories for disposition were thought to reflect differing levels of functionality given the amount and type of care required.

Propensity score matching
To overcome the inherent differences noted between the population receiving rFVIIa in the setting of TBI and those not, patients from the rFVIIa group were matched 1:2 with a similar patient not receiving rFVIIa (control). Patients were matched using the caliper (0.05) nearest neighbor matching method without replacement. Matching was based on the following demographic and

admission variables: age, sex, body mass index, history of stroke or liver disease, trauma mechanism, admission vitals, number of units of packed red blood cells (RBC) and fresh frozen plasma transfused during the initial 24 hours, Marshall score, admission GCS score, paralytic at time of GCS, Injury Severity Score (ISS), presence of inhouse neurosurgery attending, and admitting hospital. Matching produced 145 patients (96 controls, 49 treatment) that included all measure of injuries that were balanced across all variables. A subpopulation analysis of patients with primarily head injury was matched on the same variables, but with head Abbreviated Injury Scale (AIS) scores used in place of ISS. In this population, all patients with non-head AIS scores greater than 2 were excluded from matching to create a predominantly isolated head injury population. Matching within this subpopulation identified 57 patients (37 controls, 20 treatment) and balanced across all variables except time from injury to arrival (table 2).

Statistical analysis
Demographic and variables gathered on arrival in the trauma bay were compared using Pearson's χ^2 test for categorical variables, two-sample t-test for continuous or interval variables, and Kruskal-Wallis for ordinal variables. Comparison of prematching and postmatching outcome measures for rFVIIa and no rFVIIa groups was performed using Mantel-Haenszel OR for categorical variables, Student's t-test for continuous variables, and Wilcoxon rank-sum for ordinal variables. All statistical analyses were performed using Stata V.11.0. A P value of less than 0.05 was considered to be statistically significant.

RESULTS
Population characteristics
The complete data set included 4284 trauma activations, of which 501 were censored for death within 24 hours of admission. Among those succumbing to injury within 24 hours, 34 (6.8%) received rFVIIa as compared with 2.7% of initial survivors. In total 129 patients with trauma received rFVIIa, of whom 26.4% died shortly after admission and were

Table 2 Arrival vitals, injury pattern, and key early (<24 hours) laboratory values

	Prematching			Postmatching, all comers			Postmatching, primary TBI		
	−FVII (n=3366)	+FVII (n=95)	P value	−FVII (n=96)	+FVII (n=49)	P value	−FVII (n=37)	+FVII (n=20)	P value
Penetrating	5.2%	10.6%	0.020	0%	0%	1.000	0%	0%	1.000
Arrival temperature	36 (1.2)	36 (1.4)	<0.001	36 (1.1)	36 (1.2)	0.878	36 (1.2)	36 (0.6)	0.910
Arrival HR	97 (26)	96 (27)	0.747	98 (25)	97 (28)	0.821	88 (23)	88 (27)	0.968
Arrival SBP	136 (34)	130 (38)	0.099	138 (36)	138 (35)	0.985	141 (31)	149 (30)	0.344
GCS									
On arrival	6.5 (3.8)	6.6 (3.7)	0.832	5.7 (3.1)	7.1 (3.8)	0.020	7.8 (4.0)	7.9 (3.6)	0.991
At 24 hours	8.8 (4.0)	7.5 (3.6)	0.003	7.8 (3.5)	7.8 (3.6)	0.942	10.3 (3.8)	9.3 (7.3)	0.375
Time to arrival			0.058			0.914			0.021
<15 minutes	3.4	1.2		2.3	2.4		0.0	0.0	
15 minutes to 1 hour	44.4	39.5		31.0	40.5		51.9	17.6	
>1 hour to 3 hours	29.1	22.2		37.9	16.7		18.5	23.5	
>3 hours to 6 hours	10.6	14.8		12.6	16.7		14.8	23.5	
>6 hours	12.6	22.2		16.1	23.8		14.8	35.3	
ISS	27 (13)	32 (13)	<0.001	31 (14)	31 (12)	0.921	20 (9)	23 (6)	0.222
Head AIS	4.1 (0.9)	4.5 (0.6)	<0.001	4.4 (0.7)	4.5 (0.6)	0.290	4.2 (0.8)	4.6 (0.6)	0.152
Chest AIS	1.3 (1.6)	1.8 (1.8)	0.017	1.5 (1.8)	1.7 (1.8)	0.483	0.2 (0.5)	0.1 (0.4)	0.645
Abdomen AIS	0.6 (1.2)	1.1 (1.5)	<0.001	0.9 (1.3)	0.8 (1.3)	0.856	0.2 (0.5)	0.1 (0.3)	0.616
Spine AIS	0.4 (1.0)	0.7 (1.3)	0.042	0.8 (1.3)	0.9 (1.4)	0.755	0.2 (0.6)	0 (0)	0.197
Lower extremity AIS	0.8 (1.2)	1.2 (1.5)	0.012	1.2 (1.5)	0.8 (1.2)	0.103	0.2 (0.5)	0.1 (0.2)	0.138
Upper extremity AIS	0.6 (1.0)	0.8 (1.1)	0.056	0.7 (1.0)	0.9 (1.1)	0.303	0.4 (0.6)	0.2 (0.6)	0.388
INR within 24 hours	1.3 (3.3)	1.7 (0.9)	0.229	1.3 (0.5)	1.5 (0.8)	0.030	1.4 (1.0)	1.7 (1.2)	0.298
Hct within 24 hours	38 (6.7)	33 (8.6)	<0.001	33 (8)	34 (8)	0.579	34 (5)	34 (5)	0.722
Decompressive craniectomy	22.8%	44.2%	<0.001	36.5%	44.9%	0.325	24.3%	60.0%	0.008
ICP monitor	39.5%	56.8%	0.001	53.1%	63.3%	0.244	46.0%	70.0%	0.082
Initial ICP (mm Hg)	6 (11)	11 (17)	<0.001	16 (11)	13 (9)	0.203	15 (9)	12 (9)	0.379
Attending inhouse	80.4%	71.6%	0.034	77.1%	80.0%	0.730	100%	95.0%	0.661

AIS, Abbreviated Injury Score; FVII, recombinant factor VIIa; GCS, Glasgow Coma Scale; Hct, hematocrit; HR, heart rate; ICP, intracranial pressure; INR, international normalized ratio; ISS, Injury Severity Score; SBP, systolic blood pressure; TBI, traumatic brain injury.

excluded from further analysis. An additional 322 observations had no data with respect to rFVIIa administration. The final prematched cohort consisted of 3366 individuals not receiving rFVIIa and 95 admissions with rFVIIa administration (figure 1).

Individuals receiving rFVIIa were more likely to be older, female, smokers, on warfarin, and have more comorbidities than those not receiving rFVIIa (prematching, table 1). Core body temperature on arrival in the trauma bay was significantly lower in treated patients relative to prematched controls, but there was no significant difference for heart rate, systolic blood pressure, or GCS score. A greater percentage of patients arriving within 3 hours of their trauma did not receive rFVIIa, the majority presenting 15 minutes to 1 hour post-trauma. Nearly a quarter of rFVIIa recipients presented to the emergency department more than 6 hours after injury.

ISS and AIS scores were higher for recipients of rFVIIa. INR at admission was slightly elevated among those receiving rFVIIa (non-significant), and hematocrit was significantly lower than controls (38% vs. 33%, P<0.001). Patients receiving rFVIIa were more likely to have an intracranial pressure (ICP) monitor placed (39.5% vs. 56.8%, P value 0.001) or a craniectomy performed during their hospitalization (22.8% vs. 44.2%, P<0.001). Among those with ICP monitoring, the treatment group also yielded greater opening pressures relative to controls

(6 mm Hg vs. 11 mm Hg, P value 0.001). Presence of inhospital attending physician was significantly lower among those receiving rFVIIa.

Prematching outcomes
Prior to matching, treatment with rFVIIa was associated with a significantly higher likelihood of inhospital mortality (OR 3.3, CI 2.15 to 4.93; table 3). Although rFVIIa correlated with higher rates of abscess, there was no significant increase in the overall risk of complication. DVT was confirmed in 121 control and 2 rFVIIa patients (P value 0.445). No pulmonary embolisms were reported. The mean change in GCS score from admission to discharge showed less improvement among rFVIIa recipients (1.8 vs. 5.5, P<0.001), but this difference disappeared when GCS change in score from 24 hours postadmission until discharge was considered (table 4). Discharge disposition and mean hospital length of stay (LOS) were comparable between groups, whereas ICU LOS was significantly longer for those receiving rFVIIa (table 4).

Postmatching outcomes, polytrauma patients with TBI
Matching resulted in the identification of 96 controls and 49 treatment patients, and was balanced across all variables.
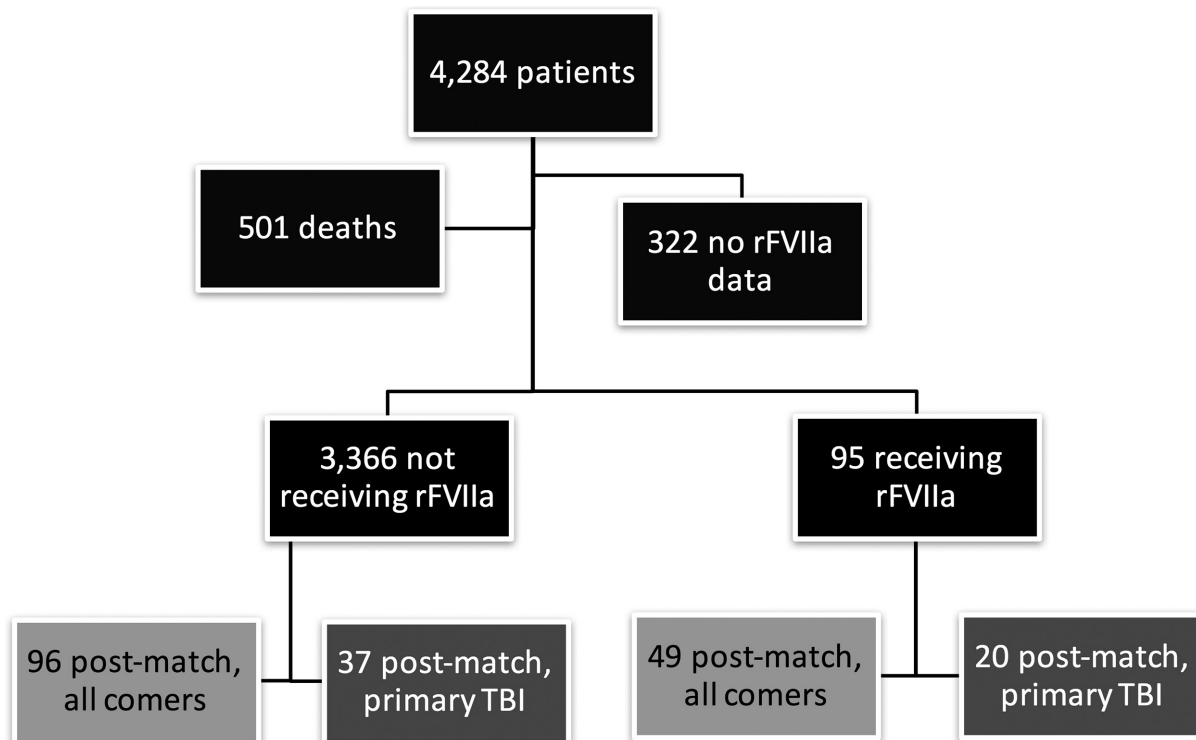
Figure 1 Study population flow diagram. rFVIIa, recombinant factor VIIa; TBI, traumatic brain injury.

The average age was 52 and 50 years, respectively, and warfarin use in each arm was 9.4% and 14.3% (table 1).

Blunt trauma accounted for 100% of admissions, and initial physiology for both groups was comparable (table 2). The average GCS score in the trauma bay was lower for those not receiving rFVIIa; however, the mean GCS score at 24 hours for both groups was 7.8 (P value 0.942). ISS as well as individual AIS scores were similar between groups. The average head AIS score indicated the presence of a critical head injury (4.4 no rFVIIa vs. 4.5 rFVIIa), whereas the mean AIS scores for other regions reflected minor to moderate injury. INR at admission was slightly elevated for both groups (1.3 vs. 1.5) and hematocrit indicative of mild anemia was 35% and 34%, respectively. ICP monitoring was common in both arms (53.1% vs. 63.3%), and

no difference in mean opening pressures or rate of decompressive craniectomy was noted (table 2).

After matching, overall mortality and morbidity did not differ between treatment groups (table 3). There were 22 deaths (22.9%) in the control arm and 15 (30.6%) in the treatment arm (P value 0.315). Complication rates were comparable between groups. The average GCS score at discharge was 12.1 for matched controls and 11.6 for matched patients receiving rFVIIa. The net change in GCS score from admission to discharge was lower in the treatment group, but again this difference disappeared when GCS score at 24 hours was used as a baseline (table 4). The rate of discharge to home or rehabilitation facility was comparable (71.2% vs. 79.4%). The mean hospital and ICU LOS did not differ significantly between groups (table 4).

Table 3 Morbidity and mortality outcomes with administration of recombinant FVIIa

	Prematching				Postmatching, all comers				Postmatching, primary TBI			
	−FVII (%)	+FVII (%)	OR	P value or 95% CI	−FVII (%)	+FVII (%)	OR	P value or 95% CI	−FVII (%)	+FVII (%)	OR	P value or 95% CI
Mortality	18.9	43.2	3.3*	2.15 to 4.93	22.9	30.6	1.5	0.69 to 3.21	21.6	20.0	0.9	0.24 to 3.48
+Craniectomy	23.1	40.5	2.3*	1.20 to 4.30	28.6	27.3	0.9	0.28 to 3.08	22.2	16.7	0.7	0.08 to 6.22
−Craniectomy	17.7	45.3	3.9*	2.22 to 6.68	19.7	33.3	2.0	0.74 to 5.66	21.4	25.0	1.2	0.19 to 7.68
Morbidity	23.6	19.0	0.8	0.45 to 1.27	33.3	22.5	0.6	0.26 to 1.28	17.1	21.1	1.3	0.31 to 5.28
VAP	12.5	9.5	0.7	0.37 to 1.47	19.8	10.2	0.5	0.16 to 1.32	2.9	0	–	–
ARDS	4.6	3.2	0.7	0.21 to 2.19	2.1	6.1	3.1	0.50 to 18.99	0	0	–	–
DVT	3.6	2.1	0.6	0.14 to 2.37	6.3	2.0	0.3	0.04 to 2.67	5.7	0	–	–
Meningitis	0.8	1.1	1.3	0.17 to 9.42	4.2	2.0	0.5	0.05 to 4.41	0	0	–	–
Abscess	0.3	2.1	8.0*	1.71 to 37.64	0	0	–	–	0	0	–	–
CRBSI	2.6	1.1	0.4	0.06 to 2.94	6.3	0	–	–	0	0	–	–

*P<0.05.

ARDS, acute respiratory distress syndrome; CRBSI, catheter-related blood stream infection; DVT, deep vein thrombosis; FVII, recombinant factor VIIa; TBI, traumatic brain injury; VAP, ventilator-associated pneumonia.

Table 4 Mean GCS, change (Δ) in GCS, hospital and ICU LOS, and disposition outcomes with administration of recombinant FVIIa

	Prematching		Postmatching, all comers		Postmatching, primary TBI	
	GCS	P value	GCS	P value	GCS	P value
Mean GCS at discharge		<0.001		0.700		0.874
−FVII	13.3 (2.5)		12.1 (2.9)		12.8 (2.6)	
+FVII	11.9 (3.3)		11.6 (3.5)		12.1 (3.4)	
ΔGCS admit to discharge		<0.001		0.001		0.400
−FVII	5.5 (4.8)		5.5 (5.3)		4.0 (4.5)	
+FVII	1.8 (5.2)		2.4 (5.6)		2.8 (4.8)	
ΔGCS at 24 hours to discharge		0.454		0.461		0.510
−FVII	3.6 (3.6)		3.8 (3.7)		1.5 (3.3)	
+FVII	3.1 (3.8)		3.1 (4.1)		1.6 (3.2)	
	Days (SD)	P value	Days (SD)	P value	Days (SD)	P value
Hospital LOS		0.921		0.397		0.940
−FVII	17.1 (20.9)		21.3 (24.0)		12.4 (10.9)	
+FVII	20.4 (31.5)		17.8 (16.3)		13.6 (14.6)	
ICU LOS		0.125		0.787		0.401
−FVII	10.1 (11.2)		13.3 (14.6)		7.6 (8.1)	
+FVII	13.5 (18.5)		12.3 (12.3)		10.3 (12.4)	
	%	P value	%	P value	%	P value
Discharge to home/rehab		0.200		0.370		0.899
−FVII	81.0		71.2		82.8	
+FVII	74.1		79.4		81.3	

FVII, recombinant factor VIIa; GCS, Glasgow Coma Scale; ICU, intensive care unit; LOS, length of stay; TBI, traumatic brain injury.

Postmatching outcomes, patients with primary TBI

Matching with selection for patients who were predominantly head-injured resulted in 37 control and 20 treated patients. Postmatch analysis revealed no significant differences in key demographic variables, including tobacco use and comorbidities (table 1). Warfarin use was 13.5% in the no-rFVIIa arm and 25.0% in the rFVIIa group (P value 0.277).

All individuals suffered blunt injuries. Vital signs on arrival were not significantly different between groups (table 2). Time to arrival was significantly longer among patients receiving rFVIIa, with over one-third presenting more than 6 hours after injury (table 2). There was no significant difference in ISS and body region AIS scores. The mean AIS score for all body regions except the head was less than 1, reflecting the large number of isolated head injury within this population. The average INR within 24 hours of arrival was slightly higher for those receiving rFVIIa than for controls (1.4 vs. 1.7), but this difference was not significant. Initiation of ICP monitoring was more frequent in rFVIIa patients, but this trend was not significant. Decompressive craniectomy was more common in patients receiving rFVIIa. Hematocrit and presence of inhouse attending were also comparable.

Mortality was 21.6% among controls and 20.0% for those treated with rFVIIa (P value 0.886; table 4). Odds of death did not differ with rFVIIa use in patients with primary TBI regardless of whether they underwent surgical decompression. Eight complications were reported in the control group as compared with four in the rFVIIa group (P value 0.292). Two patients not receiving rFVIIa developed DVT; there were no reported cases of DVT in the treatment arm. The mean GCS score at discharge was similar between groups (12.8 vs. 12.1), as was the percentage of patients discharging to home or a rehabilitation facility (82.8% vs. 81.3%). The average improvement in GCS score from admission to discharge and from 24 hours postadmission to discharge did not differ with treatment (table 4). Hospital and ICU LOS were also comparable.

DISCUSSION

rFVIIa is approved by the Food and Drug Administration for use in hemophiliacs with inhibitors, uncontrolled bleeding, or in those undergoing high-risk surgical procedures. The advantages of rFVIIa over blood products and human derived factors include its small infusion volume, room temperature storage, rapid correction of coagulation parameters, and safety profile (eg, absence of transfusion reaction and bloodborne pathogens). These characteristics have led to extensive off-label use of rFVIIa as an adjunct in the management of coagulopathy in a wide and varied number of subpopulations, including patients with coagulopathic trauma. With its ability to rapidly normalize INR, while avoiding volume overload, rFVIIa is especially attractive as a reversal agent for volume-sensitive patients with TBI or hemorrhage.

In this study the propensity score-matched analysis of a large prospectively gathered TBI database offers a statistically thorough and robust assessment of the effect of rFVIIa administration in the head-injured patient. There was no survival benefit associated with rFVIIa, a finding consistent with previous retrospective and prospective studies.[9] [13] [17-22] Additionally, rFVIIa administration was associated with significantly less improvement in GCS score from admission to discharge, and rFVIIa did not impact discharge disposition despite comparable ISS scores and inhospital complication rates. Although there was no specific measure of patient functional status at discharge, we interpret these two outcomes as indicating worsened or, at best, unchanged neurologic recovery relative to controls. Any

deleterious effect that rFVIIa may have on neurologic recovery appears to occur early, as the matched groups had comparable mean GCS scores at 24 hours after admission. To our knowledge there has been no formal evaluation of functional status after rFVIIa administration in the setting of trauma reported in the literature, and this study represents the first attempt to correlate rFVIIa use in TBI with, although crude, neurologic outcomes. When the subpopulation of patients with primary head trauma was considered, the negative effect of rFVIIa on discharge GCS score disappeared. Due to the low number of observations in the isolated TBI population, however, it is difficult to draw any definitive conclusions from this subgroup analysis.

The clinical benefit of rFVIIa with regard to correction of coagulopathy has been well documented in prior studies, but improvements in mortality and morbidity have remained conspicuously absent.[7 8 10 13 18 19 21-25] This discrepancy, along with the negative impact on GCS outcomes reported in this study, suggests that the beneficial procoagulant effects of rFVIIa may be opposed by a deleterious process acting independently from the coagulation cascade. There is a growing body of literature demonstrating the proinflammatory effects of rFVIIa.[26-28] Upregulation of proinflammatory factors may contribute to the post-traumatic inflammatory response and associated complications seen during subsequent hospitalization. Thus any clinical benefit of rFVIIa is likely more dependent on the degree of hemorrhage and coagulopathy, than on injury mechanism or severity. In the patient with exsanguinating trauma, for example, the hemostatic benefit of rFVIIa may outweigh the negative effects of augmenting an already robust inflammatory response. Selecting for a population that would most benefit from these hemostatic effects likely contributed to the results reported by Rizoli and colleagues.[20] Inclusion criteria for this study required the patient to have already received eight units of RBC prior to randomization. rFVIIa administration was associated with decreased blood product transfusion rates and a lower frequency of inhospital complications, despite no significant improvement in mortality. Although the lower incidence of MODS and ARDS among rFVIIa recipients appears to contradict the proinflammatory effects of this product described above, the reduction in exposure to immunogenic blood products relative to controls may have had an overall net positive effect.

Limited clinical trials of rFVIIa in the setting of ICH have shown mixed results. A randomized, placebo-controlled clinical trial evaluating rFVIIa use in patients not on oral anticoagulant therapy (OAT), with spontaneous ICH, reported a dose effect of rFVIIa corresponding to slowed intracranial lesion expansion.[10] This positive hemostatic effect, however, did not translate into an improvement in survival or decreased complication rates. A similar study performed in a population of traumatic ICH with known lesion $\geq 2\,mL$ on head CT also found rFVIIa to have no effect on mortality or morbidity and non-significant trend toward slowed lesion expansion relative to placebo.[29] Finally, a non-randomized, prospective study of low-dose rFVIIa administration in patients with coagulopathic (INR >1.2) TBI not on OAT reported rapid reversal of coagulopathy and reduction in the rate of ICH progression, but no survival benefit.[22] Overall, the number and quality of studies evaluating rFVIIa use in TBI are so few and limited that a Cochrane Review on the topic was unable to draw any meaningful conclusions from the existing prospective data.[7] So it may be that in patients with isolated head injuries, the ability of rFVIIa to reduce ICH expansion may not be substantial enough to mitigate its proinflammatory effects.

This study made use of retrospective data collected from 11 academic institutions with level 1 trauma designations. Limitations as to the applicability of these results must consider the retrospective nature of the analysis, as well as the generalizability of the care provided at these hospitals to other sites across the country. There was no standardized dose or protocol used for rFVIIa administration, and the indication for its use and timing of administration were not collected. Likewise, there was no standardized treatment protocol employed across centers for TBI management, which may obscure any clinical benefit from rFVIIa. Participating sites were large academic institutions, each likely to have more resources, and to provide a level of care greater than the average community hospital. rFVIIa is an expensive adjunct and might not be available at lower level or undesignated hospitals. The analysis was unable to control for antiplatelet use. Although therapeutic doses of rFVIIa may be associated with improved platelet function, its use in trauma is directed by the depletion of endogenous FVII that results from OAT use or trauma-associated coagulopathy.[30] Since rFVIIa administration would likely not be influenced by antiplatelet use, this missing variable is likely evenly distributed between matched groups in this analysis. Additionally, pre-rFVIIa and post-rFVIIa coagulation lab values were not collected. As such, the ability of rFVIIa to normalize INR, PTT, bleed time, or various TEG parameters cannot be assessed. Although it is possible that rFVIIa resulted in improved survival of a subset of more severely injured patients with TBI compared with the control group and thus resulted in a lower GCS score at discharge for the treatment group, the groups were well matched with regard to injury pattern, head CT severity, and physiology on arrival. Finally, the impact of rFVIIa on functional outcome was assessed crudely using discharge disposition and GCS score at discharge. There was no formal evaluation of patient function (eg, activities of daily living, Glasgow outcome score or functional scores), and the reported statistically significant difference in discharge GCS score may not be clinically significant.

CONCLUSION

Consistent with results from prospective and retrospective studies, this study found no clinical benefit to support routine use of rFVIIa in a patient with trauma. rFVIIa administration was associated with decreased GCS levels at discharge, suggesting a deleterious effect in this vulnerable population. Use of rFVIIa should be abandoned in the trauma.

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