Recombinant Factor VIIa: Decreasing Time to Intervention in Coagulopathic Patients With Severe Traumatic Brain Injury

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Background: Treatment of coagulopathy is often needed before neurosurgical intervention in patients with traumatic brain injury (TBI). Typically, this is accomplished with administration of plasma. We hypothesized that the off-label use of recombinant factor VIIa (rFVIIa) to normalize the coagulation profile would allow for earlier intervention than conventional therapy.

Methods: The trauma registry was used to identify patients with severe TBI who were admitted during a 4-year period and were coagulopathic at admission (international normalized ratio, INR ≥1.4) and required a neurosurgical procedure. Severe TBI was defined as head abbreviated injury scale (AIS) >3 and admission Glasgow coma score (GCS) <9. Demographics, injury, blood bank and laboratory data, time of intervention, rFVIIa use, and complications were abstracted. Characteristics of the group who received rFVIIa were compared against those treated with plasma alone with a Student's t test and χ^2 analysis, as well as nonparametric methods for comparison of medians.

Results: Of 681 patients with severe TBI, 63 were coagulopathic at admission and needed an emergent neurosurgical procedure. Twenty-nine patients who received rFVIIa were compared against 34 patients who were treated with only plasma. Mean age, injury severity score (ISS), and admission GCS and INR were not different between the two groups. Time to neurosurgical intervention was less in the rFVIIa group (median = 144 vs. 446 minutes, p = 0.0003) as were the number of units of plasma administered before intervention (median = 2 vs. 6, p = 0.0006). The rate of thromboembolic complications was not different between groups. In patients with isolated TBI, mortality was 33.3% in the rFVIIa group and 52.9% in controls (p = 0.24).

Conclusion: rFVIIa rapidly and effectively reversed coagulopathy in patients with severe TBI. rFVIIa decreased the time to intervention and decreased the use of blood products without increasing the rate of thromboembolic complications.

Key Words: Trauma, Traumatic brain injury, Coagulopathy, rFVIIa.

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Traumatic brain injury (TBI) is the leading cause of death and disability after trauma.[1] In patients with severe TBI, mortality rates ranging from 25% to 50% have been reported in the literature.[2–6] Patients with severe TBI often require immediate life-saving intervention. Emergent craniotomy for evacuation of space-occupying mass lesions may be required and, in patients without surgically amenable lesions, placement of intracranial pressure (ICP) monitoring devices is recommended to guide therapy and mitigate against secondary insults.[7]

Coagulopathy often occurs in this patient population.[8] Dilutional coagulopathy from concomitant hemorrhage, crystalloid administration, preexisting coagulation abnormalities, or preinjury use of anticoagulants often occur in the injured patient. Even in the absence of these other factors, coagulopathy can occur as the result of the brain injury itself secondary to the release of tissue thromboplastin and abnormalities of fibrinolysis.[8–11] Whatever the cause, coagulopathy in patients with severe TBI may preclude safe neurosurgical intervention. Typically, the coagulopathy is reversed with the use of fresh frozen or thawed fresh plasma. This therapy takes time to administer, however, and the large volumes of fluid needed to completely normalize coagulation may not be tolerated in older patients. Additionally, the volume of plasma required to normalize coagulation profiles in patients with severe TBI is unpredictable and exogenous replacement of factors may not be effective at achieving normalization of the clotting cascade if active hemorrhage, for example, is present.

Recombinant factor VIIa (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) is a drug developed for treatment of hemophiliacs with inhibitors to factors VIII and IX.[12,13] Because the first reports of its use in an injured soldier in 1999, rFVIIa has become increasingly utilized on an "off-label" basis as an adjunctive therapy in patients with acute traumatic hemorrhage.[14–19] Numerous case reports and series have also described the use of rFVIIa in coagulopathic and anticoagulated patients requiring emergent neurosurgical intervention for both traumatic injuries and nontrauma-related disease processes.[15,20–27] Additionally, there have been reports

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of use in patients with nonsurgical intracranial hemorrhage,[28] including one randomized trial that demonstrated efficacy of rFVIIa use in intracerebral hemorrhage.[29] A phase III multicenter follow-up to this trial has recently been completed. The results have not yet been published, but at the 16th European Stroke Conference primary outcome measures of death and disability status were disappointing as compared with earlier results.[30] This indication, therefore, remains controversial.

At the R Adams Shock Trauma Center, we have used rFVIIa on an "off-label" basis since 2001. We began using this therapy initially for acute traumatic hemorrhage and have extended our use to patients with coagulopathy and severe TBI. We hypothesized that the early use of rFVIIa in this patient population would decrease the time to neurosurgical intervention.

PATIENTS AND METHODS

After approval by the University of Maryland Institutional Review Board, the trauma registry at the R Adams Cowley Shock Trauma Center (STC) was used to identify all trauma patients admitted between July, 2002 and June, 2006 with a severe TBI (Glasgow coma score, GCS <9; head abbreviated injury scale, AIS 4 or 5). Admission laboratory data for these patients was evaluated and all patients who were coagulopathic at admission (international normalized ratio, INR ≥ 1.4) were identified. This definition of coagulopathy was chosen as a result of our current clinical practice of which patients require reversal of coagulopathy before neurosurgical intervention. The medical records of patients were then reviewed and the subjects were included for further analysis if they were deemed appropriate for immediate neurosurgical intervention at admission. During the study period, the neurosurgical management of all patients was performed by a single neurosurgeon and according to an institutional protocol based on the Brain Trauma Foundation Guidelines.[7]

At the STC, rFVIIa is requested by the treating attending surgeon, intensivist, or anesthesiologist. Release by the pharmacy requires approval of an institutional gatekeeper (TMS or RPD). The gatekeepers monitor usage and recommend dose to be given based on the clinical status of the patient. All uses of rFVIIa are recorded in a pharmacy and quality management database. Using this database, patients who met inclusion criteria for the study who received rFVIIa before neurosurgical intervention were identified. These patients were compared against those who met inclusion criteria but did not receive rFVIIa before neurosurgical intervention.

The medical records of all study subjects were then reviewed and demographics, injury-specific data, procedures performed, laboratory values, blood product utilization, length of stay, discharge disposition, and outcome data were abstracted. Timing of neurosurgical intervention was determined by time of admission compared with procedure start time as documented in the medical record. *t* Tests were used to compare differences between continuous variables and nonparametric tests were used to compare medians. χ^2 Analysis was used to compare categorical variables. A *p* value of <0.05 was considered significant for all statistical tests.

RESULTS

During a 4-year period, there were 681 patients admitted to the R Adams Cowley Shock Trauma Center with a severe TBI (GCS ≤ 8 and head AIS ≥ 4). Of these patients, 95 (13.9%) were found to be coagulopathic at admission (INR ≥ 1.4). Upon review of the medical records, 31 were excluded from further analysis as they did not have neurosurgical intervention as their brain injury was thought to be nonsurvivable. Sixty-three patients were subsequently included for further analysis. Of these patients, 29 (46.0%) received rFVIIa and 34 (54.0%) were treated with conventional therapy alone. (Fig. 1). Doses of rFVIIa administered ranged from 8 mcg/kg to 140 mcg/kg, with 18 patients receiving a single 1.2 mg dose. All but two patients received a single dose of rFVIIa with the two patients receiving two doses because of ongoing hemorrhage from concomitant injuries. There was no difference in age, ISS, Trauma Score-injury severity score (TRISS), admission Revised Trauma Score (RTS), or admission GCS in the two groups. Admission PT and INR were also similar in the two groups. There were fewer men in the rFVIIa group ($p = 0.004$), but no difference in mechanism of injury. There was no difference in the two groups in preinjury warfarin use. Sixty-two percent of subjects in the rFVIIa group had "isolated" head injuries (no other body region AIS >2), whereas 50% of the subjects who did not receive rFVIIa at admission had an isolated TBI ($p = 0.4$). Table 1 depicts the baseline characteristics of these two groups. Frequencies of associated injuries are shown in Table 2.

Neurosurgical interventions included craniotomy, intraventricular catheters (IVC), ICP monitors, or subdural drains. Mean time to neurosurgical intervention was nearly twice as long in the no rFVIIa group as compared with the rFVIIa group. Median times were evaluated to minimize the effect of outliers. In the rFVIIa group, the median time from admission to intervention was 144 minutes (interquartile range [IQR] =

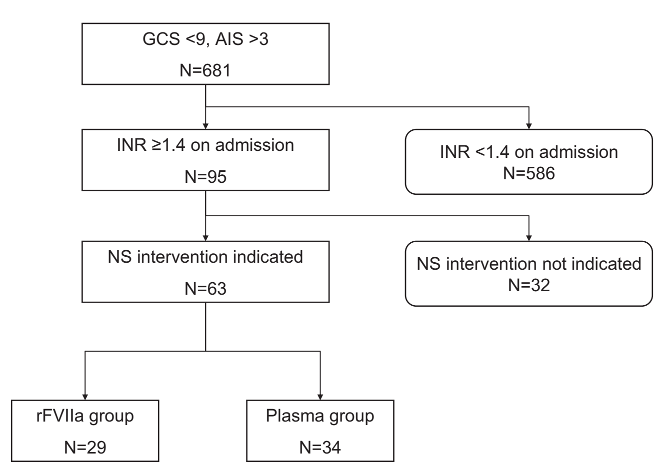

Fig. 1. *Study population.*

Table 1 Baseline Characteristics of All Patients

	rFVIIa (n = 29)		No rFVIIa (n = 34)		*p* Value
Age (years)*	39.9	25.3	38.1	19.8	0.688
ISS*	37.1	14.8	38.9	11.8	0.641
TRISS*	0.447	0.269	0.431	0.246	0.676
RTS*	4.31	0.90	4.26	0.90	0.908
Admission GCS*	4.7	1.8	4.4	1.7	0.553
Admission PT (seconds)*	17.9	4.7	16.8	3.4	0.240
Admission INR*	2.1	1.1	1.9	0.9	0.374
Male†	19	65.5	32	94.1	0.004
Blunt injury†	27	93.1	33	97.1	0.328
"Isolated" head injury†	18	62.1	17	50.0	0.394
Preinjury coumadin Use†	7	24.1	4	11.8	0.197

* Values other than *p* values are mean ±.
† Values other than *p* values are n %.
ISS, injury severity score; TRISS, Trauma Score–injury severity score; RTS, revised trauma score; GCS, Glasgow coma score; PT, prothrombin time; INR, international normalized ratio.

180) versus 446 minutes (IQR = 307) in the non rFVIIa group ($p = 0.0003$) (Fig. 2). All 64 patients had an INR rechecked before intervention. The mean INR before intervention was significantly lower in the rFVIIa group (0.8 ± 0.3 versus 1.2 ± 0.2, $p < 0.0001$). The mean number of units of plasma given before intervention was significantly less in the rFVIIa group (4.4 ± 6.6 vs. 8.5 ± 7.0 units, $p = 0.001$) as were the median number of units given (2.0 [IQR = 6.0] versus 6.0 [IQR = 6.0], $p = 0.0006$). Figure 3 depicts the percentage of patients in each group who received different numbers of units of plasma before intervention. Thirteen patients in the rFVIIa group received no plasma before neurosurgical intervention, whereas all of the non-rFVIIa patients received at least 2 units of plasma before neurosurgical intervention. Table 3 shows the differences between the two groups.

Outcome measures were examined. Outcome data for the two groups are detailed in Table 4. Length of stay (LOS) and intensive care unit LOS (ICU-LOS) trended toward being longer in the non-rFVIIa group, but these differences were not statistically significant. When patients who survived to hospital discharge were evaluated, mean LOS and ICU-LOS were 22.4 (±12.0) and 19.2 (±12.7) days in the rFVIIa group versus 27.9 (±10.4) and 25.9 (±10.2) in the no rFVIIa group ($p = 0.1$ and 0.06, respectively). Available functional outcome measures for survivors, such as discharge GCS and Rancho Los Amigos Cognitive Scale (RLAS) were the same in two groups. There was no difference in mortality rates (34.5% vs. 32.3%, $p = 0.86$).

Thromboembolic complications were recorded. The total thromboembolic complication rate for all 64 study patients was 18.7%. There was no difference in rates between the rFVIIa and non-rFVIIa groups ($p = 0.76$). Of the 29 patients in the rFVIIa group, there were two documented cerebrovascular accidents (CVA) secondary to brain herniation, one suspected CVA, one atrial thrombus, one deep venous thrombosis (DVT), and one pulmonary embolism (PE). Of the 34 patients in the non-rFVIIa group, there was one CVA, one myocardial infarction (MI), one fatal PE, and 3 DVTs. (Table 5).

Table 2 Associated Injuries of All Patients

	rFVIIa (n = 29)		No rFVIIa (n = 34)	
	n	%	n	%
Head AIS				
4	12	41.4	15	44.1
5	17	58.6	19	55.9
Face AIS				
0	14	48.3	13	38.2
1	8	27.6	7	20.6
2	4	13.8	10	24.9
3	3	10.3	4	11.8
Neck AIS				
0	26	89.7	30	88.2
1	1	3.4	1	2.9
2	0	0.0	0	0.0
3	2	6.9	3	8.8
Thorax AIS				
0	12	41.4	8	23.5
1	1	3.4	1	2.9
2	2	6.9	0	0.0
3	4	13.8	11	32.3
4	9	31.0	13	38.2
5	1	3.4	1	2.9
Abdomen AIS				
0	16	55.2	17	50.0
1	2	6.9	4	11.8
2	4	13.8	4	11.8
3	2	6.9	2	5.9
4	1	3.4	4	11.8
5	4	13.8	3	8.8
Spine AIS				
0	20	69.0	36	76.5
1	1	3.4	0	0.0
2	8	27.6	5	14.7
3	0	0.0	1	2.9
4	0	0.0	2	5.9
5	0	0.0	0	0.0
Upper extremity AIS				
0	16	55.2	14	41.2
1	3	10.3	2	5.9
2	8	27.6	12	35.3
3	2	6.9	6	17.6
Lower extremity AIS				
0	13	44.8	18	52.9
1	3	10.3	4	11.8
2	2	6.9	0	0.0
3	11	37.9	12	35.3

AIS, Abbreviated Injury Scale.

Because of the statistically insignificant, but potentially clinically significant differences in the percentage of patients with multiple injuries in the two groups, patients with isolated head injury were analyzed separately. In 35 patients with isolated head injury (all other body region AIS <2), similar variables were examined as for the group as a whole. Baseline characteristics were no different between the 18 patients who received rFVIIa and the 17 who received conventional

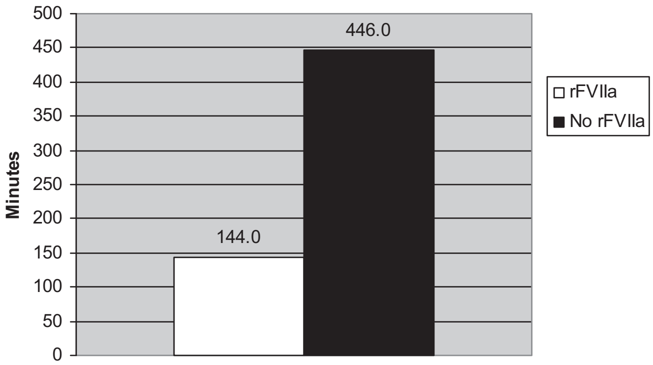

Fig. 2. *Median time to intervention in all patients.*

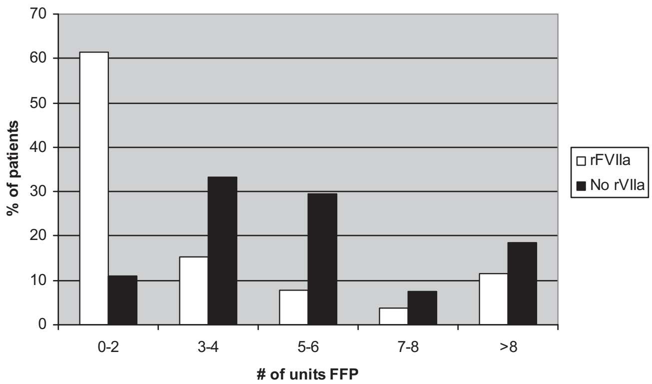

Fig. 3. *Number of units of plasma transfused before neurosurgical intervention.*

Table 3 Neurosurgical Intervention in All Patients

	rFVIIa (n = 29)		No rFVIIa (n = 34)		p Value
Time to intervention (minutes)	275.3	283.8	500.8	339.8	0.006
Plasma prior to intervention (units)	4.4	6.6	8.5	7.0	0.001
INR prior to intervention	0.8	0.3	1.2	0.2	<0.0001
Intervention type, n %					0.08
ICP Monitor	9	31.0	21	61.8	
IVC	12	41.4	6	17.6	
Craniotomy	7	24.1	6	17.6	
Subdural Drain	1	3.4	1	2.9	

Values are presented as mean ±, unless otherwise indicated.
INR, international normalized ratio; ICP, intracranial pressure; IVC, intraventricular catheter.

Table 4 Outcomes of All Patients

	rFVIIa (n = 29)		No rFVIIa (n = 34)		p Value
LOS (days)	17.6	12.9	22.1	13.0	0.185
ICU-LOS (days)	15.3	12.9	20.3	12.6	0.129
Discharge GCS	10.5	2.5	10.4	3.0	0.830
Discharge RLAS	3.7	1.5	4.3	1.7	0.226
Thromboembolic complications, n %	6	20.7	6	17.7	0.759
Mortality, n %	10	34.5	11	32.3	0.858

Values are presented as mean ±, unless otherwise indicated.
LOS, length of stay; ICU, intensive care unit; GCS, Glasgow coma score; RLAS, Rancho Los Amigos Cognitive Scale.

Table 5 Thromboembolic Complications

	rFVIIa (n = 29)		No rFVIIa (n = 34)		All (n = 63)	
	n	%	n	%	n	%
CVA	3	10.3	1	2.9	4	6.3
DVT	1	3.4	3	8.8	4	6.3
PE	1	3.4	1	2.9	2	3.2
MI	0	0.0	1	2.9	1	1.6
Cardiac thrombus	1	3.4	0	0.0	1	1.6

CVA, cerebrovascular accident; DVT, deep vein thrombosis; PE, pulmonary embolism; MI, myocardial infarction.

Table 6 Baseline Characteristics of Patients With Isolated TBI

	rFVIIa (n = 18)		No rFVIIa (n = 17)		p Value
Age (years)	49.8	26.9	44.8	20.6	0.543
ISS	27.9	7.7	30	701	0.406
TRISS	0.562	0.222	0.52	0.252	0.603
RTS	4.50	0.78	4.18	1.18	0.345
Admission GCS	5.1	1.9	4.7	1.8	0.583
Admission PT (seconds)	18.6	5.3	17.4	4.4	0.472
Admission INR	2.3	1.2	2.0	1.2	0.573
Male, n %	12	66.7	15	88.2	0.129
Blunt injury, n %	16	88.9	16	94.1	0.581
Preinjury coumadin use, n %	7	38.9	4	23.5	0.328

Values are presented as mean ±, unless otherwise indicated.
ISS, injury severity score; TRISS, Trauma Score–injury severity score; RTS, Revised Trauma Score; GCS, Glasgow coma score; PT, prothrombin time; INR, international normalized ratio.

therapy alone. (Table 6). Mean time to intervention was statistically significantly lower in the rFVIIa group than in the non-rFVIIa group as was median time to intervention (127.5 [IQR = 68] vs. 444 minutes [IQR = 306], $p = 0.0002$). Figure 4 depicts this difference. The number of units of plasma transfused before intervention was lower in the patients with isolated TBI who received rFVIIa. Eleven patients (61.1%) in the rFVIIa group received no plasma before neurosurgical intervention, whereas all 17 patients in the no-rFVIIa group received at least 2 units. Mean INR before intervention was significantly lower in the rFVIIa group. There was a difference in types of neurosurgical procedures performed in the patients with isolated TBI, with more IVC placed in patients in the rFVIIa group than in the non-rFVIIa group whereas more patients received fiber optic ICP monitors in the non-rFVIIa group. (Table 7).

In the patients with isolated TBI, mean LOS and ICU-LOS were not statistically different in the rFVIIa patients

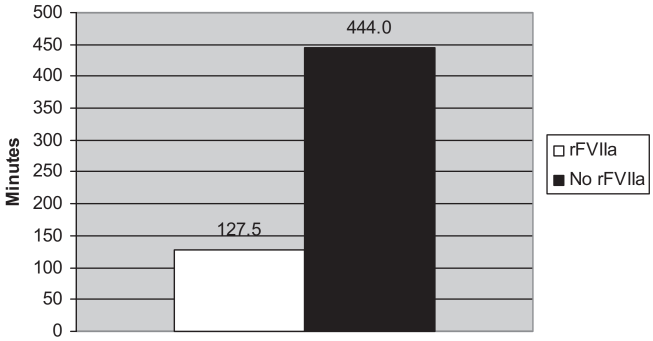

Fig. 4. *Median time to intervention in patients with isolated TBI.*

Table 7 Neurosurgical Intervention in Patients With Isolated TBI

	rFVIIa (n = 18)		No rFVIIa (n = 17)		*p* Value
Time to intervention (minutes)	185.3	219.9	518.6	409.8	0.005
Plasma prior to intervention (units)	1.5	2.2	9.3	8.3	<0.0001
INR prior to intervention	0.8	0.4	1.2	0.2	0.001
Intervention type, n %					0.03
ICP monitor	3	16.7	10	58.8	
IVC	8	44.4	1	5.9	
Craniotomy	6	33.3	5	29.4	
Subdural drain	1	5.6	1	5.9	

Values are presented as mean ±, unless otherwise indicated.
INR, international normalized ratio; ICP, intracranial pressure; IVC, intraventricular catheter.

when compared with the non-rVIIa patients, but were, on average, 5 days less in the rFVIIa group. Functional outcome measures were the same in the two groups. Mortality was not statistically significantly different in the two groups, but only 33.3% in the rFVIIa group died, compared with 52.9% in the non-rFVIIa group. In the subset of patients with isolated TBI, there were four thromboembolic complications in the rFVIIa group (two CVA resulting from herniation, one MCA territory CVA, and one atrial thrombus) and three in the non-rFVIIa group (one MCA territory CVA, one DVT, and one fatal PE). Table 8 demonstrates the differences in outcome measures in the two groups.

DISCUSSION

Coagulopathy in the patient with severe TBI occurs for a variety of reasons. Patients may have concomitant injuries causing dilutional coagulopathy from hemorrhage or the coagulation abnormalities may occur as a direct result of brain injury itself. Alternatively, many patients may be taking preinjury anticoagulants, such as warfarin, or have preexisting congenital coagulopathies. In this current study, nearly 14% of patients with severe TBI who presented to our trauma center had evidence of coagulopathy at admission. Coagulopathy in this patient population is associated with higher mortality than in noncoagulopathic patients.[9,10,12,31,32] In patients with severe TBI who were taking warfarin before injury, the mortality rate was over 90% in one recent study.[33]

rFVIIa has been used on an off-label basis as a therapeutic adjunct in the bleeding trauma patient for several years.[15–19] Additionally, numerous reports exist in the literature describing the successful use of rFVIIa for both traumatic and nontraumatic neurosurgical intervention[22–24] as well as for prevention of progression of injury in patients with nonsurgical intracranial hemorrhage.[28,29,31] rFVIIa has also been successfully used as an adjunctive reversal agent for patients with neurosurgical emergencies with premorbid anticoagulation with warfarin.[20,26,27] We present a group of severely injured patients who all had coagulopathy at admission to our trauma center. The definition of coagulopathy (INR >1.3) was chosen for this study because of the fact that this is the measured target that is used clinically at our institution. We are not aware of any evidence that specifically support this practice; however, this is the INR that our neurosurgeons require before craniotomy or monitor placement. Therefore an INR >1.3 was used to define coagulopathy for the purposes of examining the effect of rFVIIa on timing of neurosurgical intervention. The group that received rFVIIa and the group that did not were evenly matched in terms of injury severity and baseline characteristics. The only clinically significant detectable difference in the groups was the exposure to rFVIIa versus conventional reversal of coagulopathy with plasma alone.

Current recommendations in the third edition of the evidence-based "Guidelines for the Management of Severe Traumatic Brain Injury" include monitoring of ICP in all "salvageable" patients with a GCS of less than 9 and an abnormal computed tomography (CT).[7] These guidelines are based on numerous studies that have demonstrated that ICP data are useful in guiding therapy and that outcome is improved in patients who respond to targeted therapy.[34–38] Additionally, there are several studies that have documented improved outcomes in center where patients are managed by protocols which incorporate ICP monitoring.[2,39] One recent study identified late initiation of ICP monitoring to be associated with death in patients with severe TBI.[40] Delay in surgical

Table 8 Outcomes in Patients With Isolated TBI

	rFVIIa (n = 18)		No rFVIIa (n = 17)		*p* Value
LOS (days)	14.6	10.2	19.1	13.4	0.277
ICU LOS (days)	12.3	10.2	17.5	13.2	0.201
Discharge GCS	10.7	1.9	10.4	2.9	0.788
Discharge RLAS	3.7	1.4	3.9	1.9	0.782
Thromboembolic complications, n %	4	22.2	3	17.6	0.735
Mortality, n %	6	33.3	9	52.9	0.241

Values are presented as mean ±, unless otherwise indicated.
LOS, length of stay; ICU, intensive care unit; GCS, Glasgow coma score; RLAS, Rancho Los Amigos Cognitive Scale.

evacuation of extracranial mass lesions is well-known to be associated with worse, sometimes fatal, outcomes. Safe intervention is precluded by coagulopathy, however. Therefore, emergent reversal of coagulation abnormalities is essential. In the current study, the use of rFVIIa decreased the time to intervention in patients with severe TBI and coagulopathy at admission to one-third what it was in patients treated with conventional therapy alone. The reduction in time to intervention was even greater in the subset of patients with isolated TBI.

Plasma is typically used to reverse coagulopathy in the patient with severe TBI. Several studies have suggested that to prevent delays in neurosurgical intervention, empiric therapy with plasma may be indicated because of the high incidence of coagulopathy in this patient population.[31,41] Additionally, failure of rapid correction of coagulopathy in the patient with severe TBI may lead to rapid progression of intracranial injury and clinical deterioration.[31] Correction of coagulopathy with plasma may take several hours and is associated with the attendant risk of disease transmission and volume overload. Data from our institution suggest that it may take up to 12 hours to correct coagulopathy in patients who were on coumadin before injury (Ilyas et al., unpublished data). The use of rFVIIa in coagulopathic patients with severe TBI was associated with half the amount of plasma used than in conventionally treated patients. When patients with isolated head injuries were examined, the mean number of units of plasma administered before neurosurgical intervention in the rFVIIa group was one-fifth what was administered in the non-rFVIIa group. This reduction in amount of plasma transfused likely directly contributed to the decreased time to intervention, as each unit takes some time to prepare and administer, whereas the administration of a single dose of rFVIIa takes only moments. All 64 patients had effective reversal of their measured coagulopathy before intervention as determined by an INR <1.4. Since the conclusion of this study, our clinical practice has been altered and we now infrequently recheck INR before intervention because of the universal correction of the INR we have noted. This allows for even more rapid intervention as it eliminates the delay caused by drawing and waiting for results of a repeat coagulation profile. In patients treated with plasma alone, repeat coagulation profiles are still obtained before intervention because of the unpredictability of response to plasma administration.

Despite the reduction in time to intervention and number of units of plasma administered, we were unable to demonstrate a difference in mortality in this study. This may be a result of the relatively small number of patients studied or to some factor not considered in our analysis. Alternatively, but less likely, is that time to intervention is not an important variable in determination of outcome after TBI. In patients with isolated TBI, there was a trend toward reduction in mortality, from over 50% in the conventionally treated patients to 33% in the rFVIIa patients. Although this was not a statistically significant finding, it may be clinically significant. The number of patients in this study is obviously too small to draw conclusions about reduction in mortality. Similarly, we were unable to detect a difference in functional outcome at patient discharge between the rFVIIa patients and non-rFVIIa patients. In one retrospective study, neurosurgical patients treated with rFVIIa demonstrated better Glasgow Outcome Scores when compared with conventionally treated controls.[21] We were unable to validate this finding in the current study.

Although it did not reach statistical significance, LOS and ICU-LOS were close to 5 days shorter in the rFVIIa group when compared with the non-rFVIIa group. This was true for the group as a whole and for the patients with isolated TBI. When patients who died were excluded, the same findings were appreciated. Although not examined in this study, one could hypothesize that the rFVIIa patients had less "complicated" hospital courses allowing for early discharge than the conventionally treated controls. Additionally, this may explain the lack of difference in functional outcome between the two groups, as we only evaluated functional status at hospital discharge for the purposes of this study.

Thromboembolic complications after rFVIIa are a significant concern. The drug is a powerful procoagulant and may be associated with an increased risk of thromboembolic complications. In one randomized prospective trial of trauma patients with acute hemorrhage, no difference in thromboembolic complications was appreciated,[17] whereas in another randomized trial in nontrauma patients with intracerebral hemorrhage, there was an increased incidence of thromboembolic complications.[29] A recently published review of Novo-Nordisk-sponsored trials failed to detect a difference in thrombotic adverse events in patients treated with placebo versus active treatment.[42] Other studies of neurosurgical patients treated with rFVIIa failed to demonstrate an increased risk of these events,[21] whereas recent work from our own institution demonstrated an increased risk of posttraumatic cerebral infarction in TBI patients treated with rFVIIa.[43] Additional work from our institution has demonstrated an overall 9% incidence of thromboembolic complications in patients treated with rFVIIa, with one-third of those events thought to be the direct as a result of rFVIIa administration.[44] In the current study, the overall incidence of thromboembolic complications was high, but there was no difference in complication rates between the rFVIIa patients versus conventionally treated patients.

There are several significant limitations to this study. First, the retrospective design only allows for the identification of associations rather than determination of cause and effect. Additionally, our selection of INR >1.3 as the definition of coagulopathy deserves mention. Although this is the number that is used in practice at our institution, there is no specific data to support this practice. Therefore, the possibility that some of these patients had abnormal INR, but were perhaps not clinically coagulopathic could not be evaluated in this retrospective study. The study design also limited the amount of clinical information that could be compared between the two groups, such as observable differences in bleeding or reasons for procedural delays, because of the use of medical records and consistency of documented information. Additionally, the relatively small numbers in this study do not allow for determination of statistical significance of some of the outcome variables that may be clinically relevant.

Despite its limitations, this study has clearly demonstrated that in patients with severe TBI who are coagulopathic at admission, the use of rFVIIa is associated with a decreased time to neurosurgical intervention and a reduction in the use of preprocedure plasma without increasing the risk of thromboembolic complications. The difference in time to intervention may be directly the result of the elimination of the time delay in administering plasma and rechecking coagulation profiles. Further work determining efficacy and an improvement in mortality and functional outcome is needed. An appropriately powered prospective trial in this patient population has the strong potential to demonstrate a clinical benefit of FVIIa therapy.

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DISCUSSION

Dr. Peter B. Letarte (La Grange Park, Illinois): In this paper Dr. Stein et al. show us how factor VII can greatly reduce the time to the operating room for coagulopathic brain, the coagulopathic brain injured patient.

Their experience with factor VIIa matches mine and I have several questions about its use that perhaps their data can address.

First, it is my practice to use 40 micrograms per kilogram body weight dosing, the lowest dose used in the Maier intracerebral hemorrhage study to reverse coagulopathy in traumatic patients.

I have found that this dose results in the same rapid reversal of coagulopathy which you report and dramatically reduces the cost of the intervention and the subsequent sticker shock down in the pharmacy.

You used a wide range of doses. Did you find any difference in management in the different doses? And do your results confirm my empiric observation that much lower doses seem to achieve the same end?

Secondly and perhaps a related question, the secondary endpoint in this study was the reduction in the utilization of FFP. And the authors showed that less FFP was used in the factor VIIa group preoperatively.

It should be remembered that factor VIIa can wear off and that rebound coagulopathy can occur several hours after the case if steps to achieve permanent correction are not taken.

I view factor VIIa as a temporary correction, buying time to do the operation and perhaps to administer plasma at a less abusive rate. The strategies for post-op for this permanent correction of coagulopathy become the question, then.

I continue to give FFP after the factor VII is administered, which would reduce the advantage in FFP utilization. Alternatively, you could continue to give more factor VII but this might in fact be a more expensive strategy.

Have you worked out a strategy for the permanent correction of the coagulopathy? And do you have any data on how this might affect cost of using factor VIIa?

Finally, it's my practice when obtaining consent for an elderly coagulopathic patient with a traumatic intracranial bleed to tell the family the factor VIIa may allow the operation to occur but may not make any difference in the quality of the outcome.

In my experience factor VIIa allows rapid operation but often other factors besides the head injury seem to be the driving, seem to be driving the ultimate outcome for many patients.

Because of this, although factor VIIa is available to me I use it very selectively. I would be interested to see your mortality data presented in age cohorts and I would, of course, like to see long-term mortality and follow-up to assess the drug's true impact on long-term outcome.

I suspect that there are other factors confounding the impact of this drug on outcome and I think that elucidating them will contribute to its more intelligent use and wider acceptance.

I applaud this paper for starting that discussion. I believe factor VIIa will truly improve the outcome for brain injured trauma patients and I applaud the authors for leading the way in showing us how to use it intelligently.

Dr. Lawrence Lottenberg (Gainesville, Florida): Very nice paper. Looks at most of my ideas about factor VII. I have one or two questions for you.

We all know that pharmaco-therapeutics is not really controlled by us but controlled by pharmacists. Recently I got a communication from my pharmacist that over the last six months factor VIIa utilization in my institution was over $2 million. About half of that cost was made up of trauma, neurosurgery and transplant.

We also recently got communication from the federal government that Medicare will no longer reimburse hospitals for the use of factor VIIa that's off-label.

I was wondering how you are rectifying this with your use of factor VIIa. Do you know how much factor VIIa has cost you for this study? And what are we going to do about this restriction by the U.S. government about off-label pharmaco-therapeutics? Thank you.

Dr. James E. Wilberger (Pittsburgh, Pennsylvania): To echo some of those remarks, factor VII is indeed off-label use and at least to my knowledge to date there has been no study to indicate that it offers any benefit whatsoever in head injury. And, unfortunately, a retrospective study of this nature doesn't help us very much.

We also have to keep in mind that factor VII is simply factor VII. It does not correct any of the other coagulopathic problems in these patients and I think Dr. Letarte's concern about just stopping there is quite a reasonable concern.

One issue that you don't discuss in your paper, maybe you do in your manuscript, is what the neurosurgical interventions were in these patients.

A craniotomy is obviously different from an ICP monitor. And very few neurosurgeons would be hesitant to place a parenchymal ICP monitor in someone with INRs above 1.4.

Dr. Marius Keel (Zurich, Switzerland): I have just a question, do you have observed different rates of re-interventions of the craniotomies due to ongoing bleeding in the two groups? Congratulations to the study.

Dr. Deborah M. Stein (Baltimore, Maryland): Dr. Letarte, I'd like to thank you for your kind comments and insightful questions.

When we looked at the issue of dose, typically our patients with the isolated traumatic brain injury did receive a single 1.2 milligram dosing, again, the smallest unit dose vial available; whereas, those patients who were in hemorrhagic shock from concombinate injuries typically would receive a larger dose of 50 to 100 micrograms, sometimes repeated as clinical status would dictate.

We did not see a difference in terms of dose. Obviously, those patients who received 1.2 milligrams, as I stated, uniformly their INRs would reverse.

We did not see differences in clinical outcome, though, in terms of bleeding complications in the patients who received the 1.2 milligram dosing versus patients who got larger doses. But, again, those patients who got larger doses had many more concombinate injuries.

In terms of our overall FFP usage, we did not look at that for the purposes of this study; however, I will tell you that in our practice as well we give the dose of factor VII and then we proceed to give some FFP, typically at the discretion of the treating physician or the anesthesiologist.

But we do completely agree that the factor VII is a somewhat short-lived phenomenon. Typically the 1.2 milligram based on some unpublished data from our institution lasts for about six hours but, obviously, these patients are at significant risk of rebound coagulopathy, you may call it, once the factor VII wears off. So we do use FFP on an ongoing basis in those patients.

In terms of cost data, I think it's a very interesting concept to look at overall costs and overall hospital costs.

A single dose of 1.2 milligrams of factor VII costs somewhere between about $100 – I'm sorry, $1,000 to $1,200 – we wish $100 – in our institution. That is equivalent to approximately six to eight units of plasma being administered.

Again, if you combine that with length of stay data as well as potentially in terms of complications and time to OR, the cost benefit analysis may be favorable but we do not have that data right now.

As far as stratifying this data by age cohorts, I completely agree that would be a very important thing to do. Clearly, the elderly patient with the brain injury acts very differently than a young patient with a brain injury.

Unfortunately, the numbers are too small to allow for us to do that with this data. But, again, it would be a very important thing in going forward with a prospective trial.

In answer to Dr. Lottenberg's question, our institution has a pretty rigid protocol that factor VII use requires gatekeeper approval before any factor VII is administered.

I don't have any data on how much our hospital spends on factor VIIa. I am sure it is quite high. But, again, we do have this gatekeeper approval process in place by which all factor VII must be approved for use either by our hematology department or by two of my coauthors, Dr. Dutton and Dr. Scalea.

In terms of what the neurosurgical interventions were, that data is in the manuscript. There were, I believe, six craniotomies in the no factor VII group and seven craniotomies in the factor VII group.

The rest of the interventions were, in fact, intracranial pressure monitors and intra-ventricular catheters.

At our institution our neurosurgeons will not touch a patient if their INR is 1.4 or greater, whether that be for placement of a chameno or an IVC. So we do typically reverse those patients who are simply getting monitors place.

I'm sorry, I didn't hear the last question. I apologize profusely. I would be happy to answer it outside but thank you very much for your attention. And I appreciate the opportunity to present our work today.