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Factor VIIa for Correction of Traumatic Coagulopathy

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Introduction: Activated factor VIIa (FVIIa) was developed to treat hemophiliacs with high-titer antibodies to factor VIII. FVIIa initiates thrombin formation by binding with exposed tissue factor. Anecdotal reports have described the utility of FVIIa in correcting coagulopathy from trauma, but no large series exists. We present our experience with 81 coagulopathic trauma patients treated using FVIIa in years 2001-2003, compared with "control" patients matched from the trauma registry from the same time period.

Methods: Use of FVIIa was restricted to active hemorrhage with clinical coagulopathy. We recorded the cause of coagulopathy, dose of FVIIa administered, effect on clinical coagulation, pertinent laboratory values, length of stay, number and type of blood products administered, and patient outcome. For the same time period we also examined outcomes in coagulopathic patients who did not receive FVIIa.

Results: Causes of coagulopathy were diverse, and included acute traumatic hemorrhage (46 patients), traumatic brain injury (20), warfarin use (9), congenital Factor VII deficiency (2), and other acquired hematologic defects (4). Coagulopathy was reversed in 61/81 cases (75%), with an associated reduction

in PT from 19.6 to 10.8 ($p=0.000018$). 34 patients (42%) survived to hospital discharge (20/46 traumatic hemorrhage, 5/20 TBI, 4/9 on warfarin, 2/2 factor deficient, 3/4 other). Patients died from irreversible shock, multiple organ system failure, or traumatic brain injury. FVIIa patients had a higher mortality than coagulopathic controls matched by specific anatomic injuries, admission lactate value, and predicted probability of survival. Only a group identified by all three characteristics had a similar mortality to the FVIIa cohort, but the number of patients that could be matched this way was too small to be meaningful.

Conclusions: FVIIa therapy lead to an immediate reduction in coagulopathic hemorrhage in most cases, accompanied by a significant improvement in laboratory measures. Application of FVIIa as a therapy of last resort makes the identification of equivalent control patients difficult. Use of FVIIa should be considered for any patient with coagulopathic hemorrhage in which surgically-accessible bleeding has been controlled. Prospective trials of FVIIa in patients with traumatic coagulopathy are strongly indicated, and should focus on appropriate patient selection and the dose and timing of therapy.

Comments: Coagulopathy is an important complication of traumatic shock. Early exsanguination associated with coagulopathy continues to be the second leading cause of death from injury. Resuscitation with non-clotting fluids may dilute the supply of clotting factors, elevate blood pressure, reduce viscosity and washout previously formed clots. Continued bleeding leads to shock characterized by hypoperfusion, hypothermia and acidosis. Coagulopathy, acidosis and hyperthermia are the lethal triad of irreversible shock (*J Trauma* 2003; 55:39-44).

This abstract presents the largest published experience in the United States with the use of Activated Factor VIIa for coagulopathic trauma patients. Drug was given under a compassionate use guideline to patients with evidence of ongoing hemorrhage and clinical evidence of coagulopathy (bleeding from puncture sites and wound edges, expansion of existing hematomas). Routinely, patients receiving Activated Factor VIIa received 10 units of red blood cells, 8 units of plasma and a pheresis unit of platelets with continuing abnormal prothrombin time and partial thromboplastin time along with ongoing hemorrhage. Patients considered for this protocol were assessed for viability. Activated Factor VIIa was not given to patients with little hope of meeting full survival if coagulopathy was reversed.

In all, 81 patients were treated, with three-quarters of subjects receiving Activated Factor VIIa within 24 hours of admission. Average time from admission to dosage was 5.5 days in the remaining 22 patients. The majority of patients treated were victims of blunt trauma and anatomic areas of injury focused on the brain and intraabdominal organs. Forty-two percent of patients survived to hospital discharge. Best results were in the group with traumatic hemorrhage while one in four patients with traumatic brain injury and 4 in 9 patients on warfarin improved with Activated Factor VIIa. There was no evidence of myocardial infarction, ischemic stroke, pulmonary embolus or vascular graft occlusion in any patient within the first week after Activated Factor VIIa dosing. In all, three-quarters of the 81 patients were felt to show some objective sign of response to Activated Factor VIIa therapy.

The group of patients with low pH was given particular attention (*J Trauma* 2003; 55:886-891). Information from the Israeli military suggests that therapy with Activated Factor VIIa is futile in patients with a pH below 7.10. In this series, responders to Activated Factor VIIa with acute hemorrhage had an average pH of 7.29 at the time of administration versus 7.02 in patients who did not respond. However, there were 5 patients with a pH at or below 7.10 who responded to Activated Factor VIIa therapy including three long-term survivors. Clearly better clinical criteria are required to best identify patients likely to benefit from this therapy. Another group requiring careful observation is the patient population receiving traumatic brain injury. While 18 of 20 patients with traumatic brain injury responded acutely to Activated Factor VIIa therapy, long-term outcomes were poor with death in 15 of 20 patients. While this outcome may reflect the severity of brain injury, it is also possible that inappropriate microvascular response to Activated Factor VIIa may contribute to inadequate perfusion of injured brain tissue. In the discussion, the authors admit that they have limited use of Activated Factor VIIa in this population to individuals with very severe coagulopathy, facing early death from exsanguination.

Finally, the overall benefit of Activated Factor VIIa is difficult to estimate without a control group. Clearly, multicenter data with rigorous inclusion and exclusion standards is necessary to help determine optimal use of this promising but expensive therapy. In fact, these authors could not demonstrate survival benefit when Activated Factor VIIa patients were compared with large trauma population studies providing historical controls.

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Urgent Airways After Trauma: Who Gets Pneumonia?

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Background: Several risk factors, including emergent intubation, severe head injury, shock, blunt trauma, and high severity of injury, have been identified as risk factors for the development of pneumonia after trauma. This study assesses the contribution of emergent intubation to the development of pneumonia after injury.

Methods: A retrospective review of all trauma patients requiring intubation or cricothyroidotomy in the Emergency Department (ED) or in the pre-hospital area (field) over a 41/2 year period.

Results: 571 patients comprised the study population. Of these, 80% had airways established in the ED, while 20% were intubated in the field. Field intubation was associated with a lower Glasgow Coma Scale (GCS) score ($p < 0.0001$) and more severe injury ($p < 0.0001$), particularly to the chest and extremities.

Twenty-five percent of the population developed pneumonia. Patients diagnosed with pneumonia were older ($p = 0.009$), and

had a higher ISS ($p < 0.0001$), lower GCS score, ($p < 0.008$), longer ICU and hospital length of stay ($p < 0.0001$). Injuries to the head, thorax and extremities were more common ($p < 0.05$) and more severe ($p < 0.05$) in patients developing pneumonia. The incidence of pneumonia after field airway was significantly higher (35% versus 23%, $p = 0.048$).

Multiple logistic regression analysis identified field intubation, age, AIS-head, and AIS-extremity as independent risk factors for pneumonia.

Conclusions: Pre-hospital but not ED intubation is an independent risk factor for the development of post-traumatic pneumonia. Other predictors include the severity of injury, specifically head and extremity injuries.

Key Words: Trauma, Pneumonia, Head injury, Chest injury, Intubation, Aspiration, Airway.

Comments: Pneumonia is a major source of morbidity and mortality after trauma despite recent developments in antimicrobial therapy and improved critical care management practices. Recent estimates of the additional cost per patient with nosocomial and ventilator-associated pneumonia exceed \$40,000 (U.S.) in 1999 (*Chest* 2002; 122:2115-2121). This important investigation attempts to identify risk factors predicting trauma patients at increased risk for this important complication. While invasive diagnostic strategies are presented as a means to reliably make the diagnosis of pneumonia, these are labor intensive and costly (*J Trauma* 2003; 55:263-267). An opportunity to narrow the patient population at risk, where diagnostic strategies can be focused, would clearly be beneficial.

The relationship between urgent intubation and posttraumatic pneumonia reported by these authors coincides with the experience at our medical center. Patients with poorly controlled intubation, occurring in the field or under duress at outside facilities are clearly at increased risk and should be stratified in risk assessment for hospital-associated pneumonia (*J Trauma* 2004; 56:943-952). Multivariate analysis identifies severity of head and extremity injury, age and field intubation as predictive of pneumonia.

I was surprised, and the authors note that severity of chest injury and ISS in total were not predictive of pneumonia. While I agree with the authors that immobility associated with extremity injury may predispose to pneumonia, the failure of chest injury to appear as a predictive factor in multivariate analysis may reflect the constellation of injuries in the population of patients studied.

Another important observation relates to the value of intubation in the field. Patients intubated in the field had a lower Glasgow Coma Score and higher ISS, suggesting greater severity of injury and justifying early airway control. Despite these factors, patients intubated in the field had a lower mortality than those intubated in the emergency department (Arch Surg 1997; 132:592-597). Thus, early field intubation is not without complications but may be justifiable in the setting of higher injury severity.

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Decompressive Laparotomy to Treat Intractable Intracranial Hypertension after Trauma Brain Injury

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Introduction: Increases in intra-abdominal pressure (IAP) can cause increases in intracranial pressure (ICP). Recently, we noticed that abdominal fascial release could be useful in treating intracranial hypertension (ICH) after traumatic brain injury (TBI). We added this as an option in our treatment of TBI.

Methods: In our institution, ICH is treated with an algorithm using osmolar therapy, CSF drainage and barbiturates. Patients with refractory ICH have routine measurement of IAP. If elevated, consideration is given to decompressive laparotomy. We retrospectively reviewed all patients admitted from January 2000 through July 2003 who had abdominal decompression to treat refractory ICH.

Results: From 1/00 to 7/03, 17 patients underwent decompressive laparotomy for intractable ICH. Thirteen male

and 4 females all sustained blunt injury. All had failed maximal therapy including 14 who had had decompressive craniectomy. Mean ICP was 30 + 8.1 mmHg (range 20-40 mmHg) before decompression. No patients had evidence of abdominal compartment syndrome (ACS). Before decompression mean IAP was 27.5 (+ 5.2) mmHg (range 21-35 mmHg). After abdominal decompression ICP dropped precipitously by at least 10 mmHG to a mean of 17.5 (+ 3.2) mmHg (range 10-25 mmHg). In 6 patients, the decrease in ICP was transient. All died. The remaining 11 had sustained decreases in ICP. All survived made neurologic recovery and were discharged to a rehabilitation facility.

Conclusion: Decompressive laparotomy can be a useful adjunct in the treatment of ICH failing maximal therapy following TBI. More work will need to be done to precise the exact indications for this therapy.

Comments: *Intraabdominal hypertension has become a commonly recognized entity in the critical care unit (J Am Coll Surg 1995; 180:745-753; J Trauma 1998; 45:1466-1471). Elevated intraabdominal pressure adversely affects cardiac, pulmonary and renal function. Abdominal compartment syndrome occurs when pressures become significantly elevated and patients develop severe physiologic dysfunction. Treatment generally involves decompressive laparotomy or some form of release for anterior abdominal fascia to allow the viscera to bulge. This should reduce intraabdominal pressure.*

The R. Adams Cowley Shock Trauma Center reports retrospective experience with decompressive anterior fascial release in a small group of patients with elevated intracranial pressure refractory to conventional therapy including hyperventilation, mannitol administration, CSF drainage and other therapies such as high dose barbiturate administration. This study is unique in that patients underwent decompressive laparotomy solely to treat intracranial hypertension. In the past, abdominal decompression was performed secondary to elevated intraabdominal pressures. These investigators rapidly identified decrease in intracranial pressure and an overall survival of 65% in patients studied. All survivors sustained decrease in intracranial pressure after decompressive laparotomy. Most of the patients studied had passive hepatic congestion and the vast majority had one to two liters of acidic fluid at the time of abdominal wall decompression. Acute management was completed by temporary vacuum dressings. Survivors were ultimately closed with vicryl mesh and split thickness skin grafts. It is also interesting to note that central venous pressure and cardiac index were unchanged before and after abdominal decompression in this patient series.

The authors recommend decompressive laparotomy as a treatment option in the patients with intractable intracranial hypertension following head injury. Serial bladder pressure measurements should be utilized with decompression for intraabdominal pressure over 20 mmHg. This is lower than the routine threshold for significant abdominal pressure "elevation" (30 mmHg). Clearly, other standard therapies need to be exhausted prior to considering decompressive laparotomy and prospective multicenter data is required.

Electrical Injuries: A 20 Year Review

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Electrical injuries continue to present problems with devastating complications and long-term socioeconomic impact. The purpose of this study is to review one institution's experience with electrical injuries. From 1982 to 2002, there were 700 electrical injury admissions. A computerized burn registry was used for data collection and analysis. Of these injuries, 263 were high voltage (>1000 V), 143 were low voltage (<1000 V), 277 were electric arc flash burns, and 17 were lightning injuries. Mortality was highest in the lightning strikes (17.6%) compared with the high voltage (5.3%) and low voltage (2.8%) injuries, and mortality was least in electric arc injuries without passage of current through the patient (1.1%). Complications were most common in the high-voltage group. Mean length

of stay was longest in this group (18.9 + 1.4 days), and the patients in this group also required the most operations (3 + 0.2). Work-related activity was responsible for the majority of these high-voltage injuries, with the most common occupations being linemen and electricians. These patients tended to be younger men in the prime of their working lives. Electrical injuries continue to make up an important subgroup of patients admitted to burn centers. High-voltage injuries in particular have far reaching social and economic impact largely because of the patient population at greatest risk, that is, younger men at the height of their earning potential. Injury prevention, although appropriate, remains difficult in this group because of occupation-related risk.

Comments: *This large series comes from the Burn Center at Parkland Hospital in Dallas, Texas, one of the leading burn centers in the United States. The authors point out that the number of admissions occurring annually has changed little during the study period. However, the authors point out that the population of Texas has increased from 14.2 million in 1980 to 20.9 million in 2000. Thus, a lack of change could be interpreted as a decrease in the incidence of electrical injuries in the catchment area of Parkland Hospital.*

Over the past 20 years, the authors note a number of changes in evaluation and management of electrical injuries. For example, Tc- 99 pyrophosphates scintigraphy was used as a diagnostic adjunct for deep muscle necrosis. Subsequent literature has led to discontinuation of this strategy. The current diagnosis and treatment program consists of serial conservative debridement. Other changes include more liberal use of the Integra® dermal substitute (Integra LifeSciences Corporation, Plainsboro, NJ) over areas of function, such as exposed tendon. In addition, selective use of the wound VAC® Therapy™ System (Kinetic Concepts, Inc., San Antonio, TX) has resulted in enhanced wound healing. The presence of pigment in the urine following significant muscle damage is unchanged from a publication by Hunt, Sato and Baxter in 1980 (Arch Surg 1980; 115:434-438).

Finally, neurologic complications after all burn injuries have been found to be as high as 29% (Burns 1977; 3:123-125). Neurologic complications in electrical injury have been reported as high as 67% (J Trauma 1990; 10:254-258). Acute neurologic complications occurred in 5% of patients during inpatient treatment. On follow-up, however, the incidence of peripheral mononeuropathy or polyneuropathy was increased to approximately 25%. This suggests that long-term observation of these patients is essential to appropriately determine disability. Neurologic complications were most common in lightning strike victims and patients receiving high voltage injury by manmade electricity.