Acute Traumatic Coagulopathy

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Background: **Traumatic coagulopathy is thought to be caused primarily by fluid administration and hypothermia.**

Methods: **A retrospective study was performed to determine whether coagulopathy resulting from the injury itself is a clinically important entity in severely injured patients.**

Results: **One thousand eight hundred sixty-seven consecutive trauma patients were reviewed, of whom 1,088 had full data sets. Median Injury Severity Score was 20, and 57.7% had an Injury Severity Score > 15; 24.4% of patients had a significant coagulopathy. Patients with an acute coagulopathy had significantly higher mortality (46.0% vs. 10.9%; χ^2, $p < 0.001$). The incidence of coagulopathy increased with severity of injury, but was not related to the volume of intravenous fluid administered ($r^2 = 0.25$, $p < 0.001$).**

Conclusion: **There is a common and clinically important acute traumatic coagulopathy that is not related to fluid administration. This is a marker of injury severity and is related to mortality. A coagulation screen is an important early test in severely injured patients.**

Key Words: **Traumatic coagulopathy, Hypothermia, Fluid administration.**

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Coagulopathy after trauma is common but is usually attributed to dilution from intravenous fluid therapy, massive blood transfusion, progressive hypothermia, and acidosis. There are few studies that examine the state of the hemostatic system immediately after injury, before resuscitation, and before the onset of hypothermia and acidosis.

The release of mediators after tissue trauma activates multiple humoral systems including the coagulation, fibrinolysis, complement, and kallikrein cascades. These in turn have wide-ranging effects on neutrophils, macrophages, platelets, and other cellular elements, which provoke a multitude of changes in the body's hemostatic mechanisms. These same mechanisms are implicated in the development of the systemic inflammatory response syndrome and multiple organ failure.[1] Certain injuries in particular are known to interfere with the coagulation system. Brain injuries have been shown to lead to coagulopathy, caused in part by release of brain tissue thromboplastins after neuronal injury.[2,3] Similarly, long bone fractures may be associated with disorders of the hemostatic mechanisms.[4]

This study was designed to determine whether a clinically important acute coagulopathy exists after trauma, before and independent from that caused by fluid replacement therapy. Acute traumatic coagulopathy might be related to injury severity and have an effect on outcome. We retrospectively analyzed the results of the immediate clotting screen sample taken from multiple trauma patients on arrival in the emergency department.

PATIENTS AND METHODS

Data were collected on all patients admitted via our helicopter emergency medical service. This subset of the hospital trauma database was used, because there is physician control of the prehospital phase and better documentation of this period, including the type and amount of fluids administered. Data were collected prospectively on patient demographics, time from injury to arrival in the emergency department, and fluid administration at scene; and on anatomic injury characteristics, scored using the Abbreviated Injury Scale (AIS).[5] The Injury Severity Score (ISS) was calculated from these data.[6]

According to protocol, on the arrival of the patient in the emergency department, the first task of one member of the trauma team is to take an arterial blood sample via a direct puncture, with a nonheparinized syringe. Prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) were determined from this sample, and represent the coagulation state before further resuscitation. The coagulation data were collected retrospectively from the hospital's laboratory computer database.

The presence of a coagulopathy was defined as a PT over 18 seconds, APTT over 60 seconds, or TT over 15 seconds (1.5 times normal). These values are taken from the British National Blood Transfusion Service and the American College of Pathologists' guidelines and indicate a coagulopathy requiring blood product replacement therapy in the presence of active or impending hemorrhage.[7,8]

Mortality was used as the outcome measure. We analyzed the relationships between coagulopathy and injury characteristics, fluid administered, and outcome using univariate and multivariate regression analyses in Microsoft Excel

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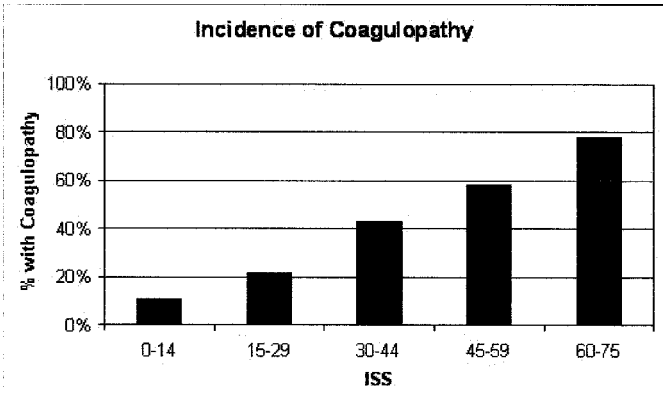

Fig. 1. *Incidence of coagulopathy. ISS, Injury Severity Score.*

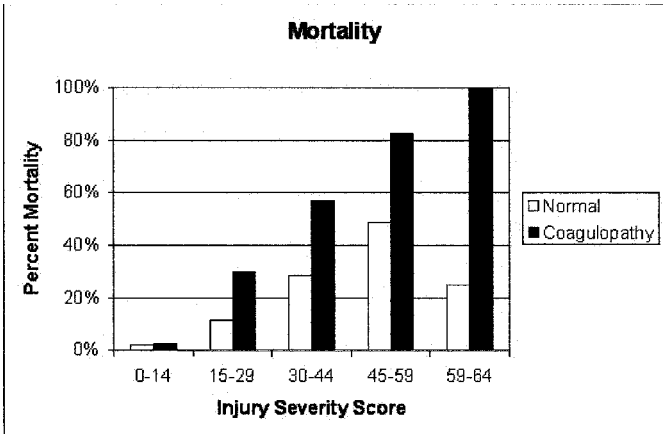

Fig. 2. *Mortality.*

and Arcus Quikstat software packages. A value of $p < 0.05$ was taken to represent statistical significance.

RESULTS

For the years 1993 to 1998, 1,867 patients were admitted via the helicopter emergency medical service. An immediate coagulation screen was available on 1,088 patients. Median age was 30 (interquartile range [IQR], 22–50). The male-to-female ratio was 2.9:1 and 75% of injuries were attributable to blunt trauma.

The median time from injury (estimated as the time the emergency services were alerted) to arrival in the emergency department was 73 minutes (IQR, 57–75); 24.4% of patients had a coagulopathy at admission, 16.3% had a PT over 18 seconds, 13.1% an APTT over 60 seconds, and 14.2% a TT over 15 seconds. There was no relationship between age of the patient and the incidence of coagulopathy. Mechanism of injury also did not affect the incidence of coagulopathy.

The overall mortality rate was 19.5%. Patients with a coagulopathy at admission had a mortality of 46.0%, significantly different from 10.9% for those with normal clotting (χ^2, $p < 0.001$).

The median ISS was 20, with 57.7% of patients having an ISS over 15. Although only 10.8% of patients with an ISS of 15 or below had a coagulopathy, 33.1% of those with an ISS over 15 presented with a clotting disorder. This figure increased to 61.7% for those with an ISS over 45 (Fig. 1). In a multiple regression analysis, coagulopathy was associated with an increased mortality over and above that of injury severity as measured by ISS ($p < 0.001$, $r^2 = 0.3$). This is detailed in Table 1 and illustrated in Figure 2, comparing patients with and without coagulopathy across the range of injury severity.

Patients received a median of 800 mL (IQR, 250–1,500 mL) of intravenous fluid in the prehospital phase of care. One hundred twenty-two patients received no fluids, 584 patients received crystalloid, and 405 received colloid. For those patients receiving fluids, median values were 500 mL (IQR, 500–1,000 mL) for crystalloid and 1,000 mL (IQR, 500–1,500 mL) for colloid. Patients with coagulopathy received a median of 700 mL (IQR, 200–1,500 mL) and those without 1,000 mL (IQR, 300–1,500 mL) of fluid. Using univariate analyses, there was no significant correlation between the amount of fluid administered and the development of a coagulopathy ($p = 0.37$, $r^2 < 0.01$). The volume of colloid administration was also not related to the incidence of coagulopathy, regardless of injury severity.

The relationship between AIS scores in different body regions and the presence of coagulopathy was analyzed in a multiple regression analysis. The incidence of both coagulopathy and mortality increased as injury severity increased in the head, chest, abdomen, limb, and external ISS body regions, and this was not related to the amount of fluid administered ($p < 0.001$, $r^2 = 0.25$). An analysis of patients with single body region injury (AIS score of 2 or more in specified region, AIS score of 0 or 1 other body regions) showed 8.8% of head (13 of 148), 22.9% of chest (16 of 70), 16% of abdominal (4 of 25), and 20.5% of limb injuries (23 of 112)

Table 1 **Incidence of Coagulopathy and Mortality by ISS[a]**

	ISS 0–14		ISS 15–29		ISS 30–44		ISS 45–59		ISS 60–74	
	Norm.	Coag.	Norm.	Coag.	Norm.	Coag.	Norm.	Coag.	Norm.	Coag.
No.	380	46	308	83	94	70	37	52	4	5
Died	8	1	36	25	27	40	18	43	1	5
Mortality (%)	2.1	2.2	11.7	30.1	28.7	57.1	48.6	82.7	25.0	100.0

[a] Norm., normal; Coag., coagulopathy.

presented with a coagulopathy. No patient with an isolated face or external injury had disordered coagulation on arrival.

In most cases, missing data were attributable to a coagulation profile not being taken in the emergency department. Patients with missing data were similar regarding age, sex, and mechanism of injury. However, they were less severely injured, with lower ISS scores (median, 9; IQR, 1–28) ($p < 0.001$, *t* test). Of the missing patients, 35.6% had an ISS > 15 versus 57.7% of those in the study group.

DISCUSSION

Nearly one quarter of the trauma patients studied arrived in the emergency department with an established coagulopathy. These patients received only minimal resuscitation in the field, and the presence of coagulopathy did not correlate with the amount or type of intravenous therapy administered. Apart from fluids, only anesthetic and analgesic medication is administered and none of those used by the prehospital team are known to affect clotting function.

The high Injury Severity Scores of this patient population may be responsible for the high rate of coagulopathy at admission. As the level of tissue trauma increased (rising ISS), the incidence of coagulopathy increased, such that nearly two thirds of patients with an ISS > 45 arrive with a significant derangement of their hemostatic mechanisms. Those patients with coagulopathy were more likely to die than those without for a given degree of injury. Trauma patients with coagulation abnormalities are known to develop organ dysfunction and spend longer on the intensive care unit.[9,10] The Injury Severity Score may be underestimating the volume of tissue injury sustained, because significant injuries may not be reflected in the ISS of a patient with multiple injuries.

Although we have not shown cause and effect, our results are consistent with the theory that trauma results in the release of factors that are responsible for the development of a clinically significant coagulopathy. A variety of cellular and humoral mechanisms are likely to be involved in this process, leading to a combination of consumption coagulopathy, excessive fibrinolysis, and activation of inflammatory pathways. Tissue injury leads to the release of tissue factor, which activates the coagulation pathways. Extensive tissue factor release, resulting in widespread or systemic activation, results in a consumption coagulopathy.[11,12] Excessive fibrinolysis may also be a result of extensive tissue trauma.[13,14] Inflammatory mediators have been implicated in activation of the coagulation pathways. The development of an acute coagulopathy may therefore be an indicator of loss of regulation of the local inflammatory response and represent the initiation of the systemic inflammatory response syndrome and its sequelae.[15–17]

Specific injuries are known to lead to disorders of hemostasis and thrombosis. Brain injury leads to a disseminated intravascular coagulation resulting from the thromboplastic activity of brain tissue that enters the circulation.[3,18] Multiple long bone fractures are also associated with disturbances of coagulation, as in our study.[4,19]

The results of this study may be biased by the lack of a coagulation profile in the missing patient group, who had lower Injury Severity Scores. The incidence of coagulopathy among all trauma patients, including those with minor injuries, is probably lower than that found in our study.

The study also does not examine the possibility that preexisting medical conditions or therapy may be responsible for the measured acute coagulopathy. Data on preexisting disease and medication are difficult to collect in severely injured patients, and especially in those patients who die.

Although it is possible that some patients may have had significant liver disease or had been taking anticoagulant medication, the young population and wide catchment area of this study would suggest that these would represent a small proportion of the patients. This is further justified by the lack of a relationship between age and the incidence of coagulopathy.

Although we have not shown cause and effect, it would seem that tissue trauma results in the release of mediators that are responsible for the development of a clinically significant coagulopathy. This response is proportional to the severity of injury. A variety of cellular and humoral mechanisms are involved, leading to a combination of a procoagulant state, excessive fibrinolysis, and activation of inflammatory pathways.

CONCLUSION

Coagulopathy is common in trauma patients. Medical intervention may then augment this coagulopathy by hemodilution with large fluid volumes, the administration of colloids,[20,21] massive transfusion with stored blood, and the subsequent development of hypothermia.[22,23]

However, there is an acute coagulopathy, before significant fluid administration, that may be attributable to the injury itself. This derangement reflects the severity of tissue damage and carries a worse prognosis. The presence of an early coagulation abnormality has implications for both management and outcome. With such a high proportion of patients with multiple injuries arriving in the emergency department with an established clotting disorder, we would suggest that a coagulation screen is an important early laboratory test in the severely injured patient. However, it is important to appreciate how coarse these basic tests are in reflecting the true state of the body's hemostatic mechanisms.

REFERENCES

1. Schlag G, Redl H. Mediators in trauma. *Acta Anesthesiol Belg.* 1987;38:281–291.
2. Olson JD, Kaufmann HH, Moake J, et al. The incidence and significance of hemostatic abnormalities in patients with head injuries. *Neurosurgery.* 1989;24:825–832.
3. Hulka F, Mullins RJ, Frank EH. Blunt brain injury activates the coagulation process. *Arch Surg.* 1996;131:923–927.

4. Hofmann S, Huemer G, Kratochwill C. Pathophysiologie der Fettembolie in der Orthopadie und Traumatologie. *Orthopade.* 1995; 24:84–93.
5. Association for the Advancement of Automotive Medicine. *The Abbreviated Injury Scale, 1990 Revision.* Des Plaines, IL: Association for the Advancement of Automotive Medicine; 1990.
6. Baker SP, O'Neill B, Haddon W, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma.* 1974;14:187–196.
7. Hewitt PE, Machin SJ. Massive blood transfusion. In: Contreras M, ed. *ABC of Transfusion*. London: BMJ Publishing Group; 1992:38–40.
8. College of American Pathologists. Practice parameters for the use of fresh frozen plasma, cryoprecipitate and platelets. *JAMA.* 1994; 271:777–781.
9. Blamback M. Blood coagulation and fibrinolytic factors as well as their inhibitors in trauma. *Scand J Clin Lab Invest.* 1985; 178(suppl):15–23.
10. Gando S, Kameue T, Nanzaki S, et al. Participation of tissue factor and thrombin in posttraumatic systemic inflammatory syndrome. *Crit Care Med.* 1997;25:1820–1826.
11. Gando S, Tedo I, Kubota M. Post-trauma coagulation and fibrinolysis. *Crit Care Med.* 1992;20:594–600.
12. Gando S, Nanzaki S, Sasaki S, Kemmotsu O. Significant correlations between tissue factor and thrombin markers in trauma and septic patients with disseminated intravascular coagulation. *Thromb Haemost.* 1998;79:1111–1115.
13. Risberg B, Medegard A, Heideman M, et al. Early activation of humoral proteolytic systems in patients with multiple trauma. *Crit Care Med.* 1986;13:917–925.
14. Enderson BL, Chen JP, Robinson R, Maull KI. Fibrinolysis in multisystem trauma patients. *J Trauma.* 1991;31:1240–1246.
15. Gando S, Nakanishi Y, Tedo I. Cytokines and plasminogen activator inhibitor-1 in posttrauma disseminated intravascular coagulation: relationship to multiple organ dysfunction syndrome. *Crit Care Med.* 1995;23:1835–1842.
16. Gando S, Nanzaki S, Morimoto Y, et al. Systemic activation of tissue-factor dependent coagulation pathway in evolving acute respiratory distress syndrome in patients with trauma and sepsis. *J Trauma.* 1999;47:719–723.
17. Gando S, Kameue T, Nanzaki S, et al. Participation of tissue factor and thrombin in posttraumatic systemic inflammatory syndrome. *Crit Care Med.* 1997;25:1820–1826.
18. Miner ME, Kaufmann HH, Graham SH, et al. Disseminated intravascular coagulation fibrinolytic system following head injury in children: frequency and prognostic implications. *J Paediatr.* 1982; 100:687–691.
19. Kunz F. Plasma lipids, coagulation factors and fibrin formation after severe multiple trauma and an adult respiratory distress syndrome. *J Trauma.* 1971;18:115–120.
20. Brazil EV, Coats TJ. Sonoclot coagulation analysis of in-vitro haemodilution with resuscitation solutions. *J R Soc Med.* 2000; 93:507–510.
21. Jamnicki M, Zollinger A, Seifert B, et al. The effect of potato starch derived and corn starch derived hydroxyethyl starch on in vitro blood coagulation. *Anaesthesia.* 1998;53:638–644.
22. Krause KR, Howells GA, Buhs CL, et al. Hypothermia-induced coagulopathy during hemorrhagic shock. *Am Surg.* 2000;66:348–354.
23. Watts DD, Trask A, Soeken K, et al. Hypothermic coagulopathy in trauma: effect of varying levels of hypothermia on enzyme speed, platelet function and fibrinolytic activity. *J Trauma.* 1998;44:846–854.