Trauma and Coagulopathy

A New Paradigm to Consider

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Injury, intentional and unintentional, is one of the main causes of death for adult Americans.[1] Further, from 1999 to 2003, injury was the main cause of premature mortality (measured as potential years of life lost), ahead of malignancy and heart disease, for Americans who died before their 65th birthday.[2] Injuries that cause massive hemorrhage are often associated with the highest mortality rates. More than 50% of patients who present with massive hemorrhage die, and for those who die within hours of the injury event, it is often the most common cause of death.[3]

Over the past 3 decades, as trauma systems and designated trauma centers developed and matured, there has been a continual drop in the injury mortality rate in America. In the state of Georgia, the age-adjusted all-injury mortality rate has dropped 29% in 20 years, from 1981 to 2000.[4] Trauma centers have been effective in treating massive hemorrhage that is surgically correctable with timely and appropriate care. The preventable death rate has reduced from 40% 30 years ago to less than 5% in the modern trauma center.[5]

See Invited Critique at end of article

Contrast this to the situation over the past 10 years in America, where the age-adjusted mortality rate from 1993 to 2003 has not changed significantly from the 55.9 deaths per 100 000 population recorded for 2003.[6] After severe brain injury, these trauma deaths continue to be caused mainly by massive hemorrhage.[7] However, these cases of death from massive hemorrhage are commonly due to nonsurgical bleeding or trauma-related coagulopathy, the treatment of which remains widely varying and often ineffective.

Therefore, there is a need to find new effective treatments for trauma-related coagulopathy. But new approaches will continue to elude us if our understandings of the underpinnings of this coagulopathy are not accurate. In this article, I will present a summary of recent evidence that shifts the paradigm of understanding of how trauma-related coagulopathy develops. An accurate shift would allow research and intervention strategies to follow directions that could start to reduce trauma deaths from massive hemorrhage. We will review the coagulopathy mechanisms as they are presently understood and then show how these mechanisms tie together with new hypothesis-generating research to form a new paradigm that, if confirmed, may be superior and more appropriate to delineate trauma-related coagulopathy mechanisms and, thereby, treatments.

MASSIVE HEMORRHAGE AND METABOLIC FAILURE

Patients with massive hemorrhage, when it is uncontrolled for any length of time, often develop metabolic failure, more commonly referred to as the "triad of death": hypothermia, acidosis, and coagulopathy. In the present paradigm, coagulopathy and ongoing hemorrhage are both contributor and outcome of the metabolic failure, which carries a high mortality rate. In one series of more than 17 000 trauma patients, 82% of early in-hospital deaths were attributed to metabolic failure.[8] Cos-

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griff et al[9] showed that the presence of hypothermia and acidosis in a bleeding patient predicts the development of life-threatening coagulopathy and that combinations exponentially increased the occurrence up to 98% if all 4 factors, hypotension, Injury Severity Score higher than 25, hypothermia, and acidosis, were present.[9] Consequently, interventions such as the abbreviated or "damage control" laparotomy are routinely used to aggressively treat hypothermia, acidosis, and blood loss first rather than extended surgical repairs of anatomical injuries. This approach has been reported to increase survival in the range of 20% to 60%.[10,11] Therefore, an important interplay between these 3 factors, acidosis, hypothermia, and coagulopathy, appears to occur in the patient with massive blood loss culminating in a severe clinical coagulopathy and a nonsurvivable metabolic deterioration and death. In our present concept of the development of trauma-related coagulopathy, how does each of these 3 factors relate?

The relationship of hypothermia to the development of coagulopathy is demonstrated both in vitro and clinically in patients. A lowered temperature can impair platelet aggregation and decreases function of coagulation factors in nondiluted blood.[12,13] Clinically, Rohrer and Natale[14] showed that patients with a temperature lower than 34°C had elevated prothrombin (PT) and partial thromboplastin (PTT) times. They were also able to show a linear relationship between the elevation in the coagulation profile times and the drop in the patient's core temperature.[14] These studies substantiate the importance of an association between hypothermia and coagulopathy but uncontrolled cohort studies defy the scientific ability to determine a cause-and-effect conclusion in the setting of severe injury.

Acidosis, which occurs in the setting of trauma as a result of bleeding and hypotension, also contributes to the failure to clot. Animal studies have shown that a pH less than 7.20 is associated with impaired hemostasis.[15] Blood from healthy volunteers subjected to an acidic environment showed a number of coagulation enzyme system changes as well as platelet dysfunction.[16,17] In patients, it has been shown that the presence of acidosis is one of the strongest risk factors for the development of life-threatening hemorrhage in a patient who has received massive transfusions.[9] Even therapeutic options, such as factor VIIa, have been shown to be less effective in a low pH environment.[16]

From studies such as these, the concept was promoted that coagulopathy is a secondary phenomenon developing after severe hemorrhage in the presence of hypothermia and acidosis. This model is often referred to as "the bloody vicious cycle."[9] Retrospective cohort studies of trauma patients who have received massive transfusions show mortality rates of 62% to 77%, where the massive transfusion acts as a surrogate for severe hemorrhage. These patients were more likely to die of their severe hemorrhage, in the face of hypotension, hypothermia, and acidosis, if they had developed clinical microvascular bleeding than if they had no clinical coagulopathy.[18-20] Therefore, coagulopathy, as it develops in the face of ongoing hemorrhage, hypothermia, and acidosis, carries a high mortality rate. However, there are no prospective studies nor well-controlled retrospective studies that attempt to delineate the contribution of these various factors. This is consistent with clinical observations that neither coagulopathy nor survival is predictable based on hypothermia and acidosis alone. Therefore, this model of the bloody vicious cycle is an inadequate explanation for posttraumatic coagulopathy.

SECONDARY CAUSES OF TRAUMA-RELATED COAGULOPATHY

Even with or without hypothermia and acidosis, posttraumatic coagulopathy can develop in a substantial number of patients. In these patients, the 3 most widely held and best-documented postulates to explain the development of recalcitrant coagulopathy after trauma are dilution, depletion, and disseminated intravascular coagulation (DIC). Iatrogenically, resuscitation with crystalloid and blood replacement with packed red blood cells are believed to lead to clinically significant dilution of important coagulation system components. Second, the active loss of blood due to injury is believed to add significantly to the deletion of needed components of the clotting system to allow the body to clot at the site of injury. Last, the development of DIC has been documented in a subset of trauma patients and has been put forward as the pathway by which late sequelae, such as multiple-organ failure, occur among those who survive past the initial period of treatment. There are in vitro, animal, and human data to support each of these hypotheses and their role in posttrauma coagulopathy. But the interplay of these 3 factors in the face of the dynamic processes of ongoing blood loss and concurrent blood replacement is not fully understood.

Dilution

Ongoing blood loss is replaced, at least initially, with crystalloid solutions. Therefore, it is intuitive that dilution of the clotting factors and platelets can occur. Hewson and colleagues[21] investigated the contribution of crystalloid over and above blood replacement in trauma patients who received transfusions of 10 or more units of blood. They showed that the elevation of the PTT was correlated with the number of liters of crystalloid received by the patient. Faringer and his colleagues[22] found that admission PT and PTT were more commonly elevated in patients who received prehospital resuscitation with crystalloid as compared with those who did not, despite mechanism of injury. These well-cited studies are only correlational in association and fail to control for many of the other known prognostic factors for outcome. Despite the wide adoption of this concept of dilution and its "common sense" appeal, strong evidence for a major role in the development of posttrauma coagulopathy is lacking.

Colloid has been implicated in coagulopathy by mechanisms other than dilution. It has been shown in porcine liver injury models to cause coagulopathy when the blood volume is replaced by up to 65% of the total with a colloid solution and the coagulopathy will correct in correlation with the amount of fibrinogen replacement administered.[23] In blood collected from human volunteers, the same authors showed, using the thromboelasto-

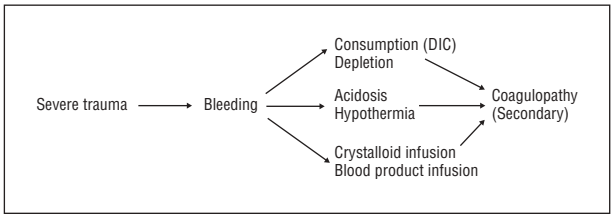

Figure 1. Simplified illustration of posttraumatic coagulopathy as a secondary or resultant event. DIC indicates disseminated intravascular coagulation.

gram, that colloid had a dramatic effect on both the time to form a clot and its tensile strength.[24] These changes were most marked for the colloid solutions as compared with crystalloids. Consequently, colloid as a resuscitation fluid is no longer commonly used by trauma centers or hospitals that follow Advanced Trauma Life Support protocols.

Depletion

As well as the concept of dilution of clotting factors, a similar rational explanation is the role of depletion of the clotting factors by ongoing bleeding that far exceeds production or reserve of the coagulation system. This depletion is further exacerbated by the administration of packed red blood cell transfusions. Therefore, clinicians have postulated that posttraumatic coagulopathy could be prevented by prophylactic transfusion of fresh frozen plasma and platelets. However, multiple authors have tried without success to elucidate the appropriate ratio of transfused units of packed red blood cells to fresh frozen plasma that should be administered to prevent the development of life-threatening coagulopathy.[19,25-27] The various fresh frozen plasma–blood product replacement ratios presently used were determined from studies that involved elective surgery patients in normovolemic situations to estimate the degree of hemodilution.[28] Further, Reed and colleagues[29] showed that neither prophylactic platelet transfusion nor the presence of thrombocytopenia was correlated with prevention or subsequent development of coagulopathy. Therefore, the evidence to date does not confirm the inference that depletion is a major player in posttrauma coagulopathy. There remain multiple unanswered questions about the interplay of blood loss with blood replacement volume, rate, the reduction of platelets and coagulation factors, and the type of blood product required in both amount and rate. However, more recent evidence from Iraq suggests that early factor and platelet replacement may play a role in allowing the body to adequately clot after injury and even improve survival.[30]

Disseminated Intravascular Coagulation

Recent studies have implicated DIC as an important posttrauma sequela that results in coagulopathy and, consequently, multiple organ failure. As early as 1970, Hardaway[31] showed that multiple intravascular thrombi associated with areas of focal necrosis in various vital organs consistent with the pathological picture of DIC were found in the autopsies of trauma patients. Gando and colleagues[32] have done extensive work showing that DIC develops in a subset of injured patients and is associated with the occurrence of systemic inflammatory response syndrome and multiple organ failure. Gando et al and others have shown that this subset of patients who go on to meet DIC criteria show the normal activation of coagulation that occurs after trauma but there is a suppression of normal anticoagulant pathways and impaired fibrinolysis leading to DIC and the increased risk of systemic inflammatory response syndrome and multiple organ failure.[33-37]

Spahn and Roissant, in a recent review article,[38] have summarized the present model of posttraumatic coagulopathy. It discusses the unidirectional interplay of the factors we have discussed, hypothermia, acidosis, dilution, depletion, and DIC, promoting the concept that the development of microvascular bleeding is a secondary event (**Figure 1**). However, from experience, trauma specialists know that the patients, the clinical circumstances, and the outcome with posttraumatic coagulopathy are diverse and do not easily fit a unidirectional model, despite the universally high mortality rate. Despite identification of these factors, we still are unable to reliably predict who will develop coagulopathy, to what severity, and who will ultimately die despite replacement treatment. The present paradigm raises as many questions as it answers. New research has investigated the epidemiology of coagulopathy from the time of injury to attempt to clarify the role of these factors and to possibly identify others in the development of posttraumatic coagulopathy.

COAGULOPATHY AS AN INDEPENDENT PREDICTOR OF MORTALITY

Three recent epidemiological studies from America and Europe have analyzed trauma registry data to describe posttrauma coagulopathy from injury event. The first study, from a level I trauma center in Miami, Florida, showed that up to 25% of trauma patients on arrival at a hospital already have an abnormal coagulation profile.[39] It further correlated this finding of early posttrauma coagulopathy with a lower survival. A cohort of 20 103 trauma patients was retrospectively analyzed using a logistic regression to confirm the relationship of coagulopathy to mortality while controlling for known prognostic factors.[39] Using the admission coagulation profile, it was shown statistically that an abnormal PT or PTT was an independent predictor of mortality, with an increased risk of death of 35% and 426% as compared with the mortality rate in patients with a normal PT and PTT, respectively. This relative increase was present even after controlling for presently understood causative factors, including head injury.

A similar analysis was performed in 2 further studies, 1 in England and 1 in Germany. All 3 studies correlated initial or early coagulation profile with patient outcome. In Germany in 2001, Rixen et al[40] reviewed 2069 patients and found that PT was statistically significantly associated with outcome in a multiple linear regression model controlling for other known prognostic factors. The third study,[41] by Brohi et al published in June 2003,

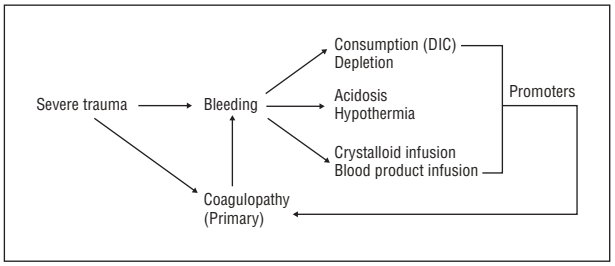

Figure 2. Simplified illustration of posttraumatic coagulopathy as a primary event modified by promoters. DIC indicates disseminated intravascular coagulation.

showed very similar results, with the incidence of an abnormal first PT or PTT being independently associated with the outcome of death, even controlling for crystalloid or colloid administration.

These studies suggest a shift in the paradigm presently used to explain posttraumatic coagulopathy (**Figure 2**). If coagulopathy appears immediately postinjury in a subset of patients, then it cannot be explained simply by the present paradigm with its factors as a secondary phenomenon.

However, one last prevalent idea remains that supports the present paradigm that coagulopathy is secondary to other processes: It is commonly held that coagulopathy is "caused" by head injury.

TRAUMATIC COAGULOPATHY AND HEAD INJURY

A number of cohort studies have been used to show that coagulopathy occurs after the release of thromboplastin from patients with brain injury. However, Gando et al[42] have shown that there is no coagulofibrinolytic difference between patients with or without head injury.

Further, these cohort studies have a number of significant methodological flaws. They are mainly retrospective in design with significant selection bias. They have used inappropriate comparison groups, such as neurosurgical noninjured patients compared with injured patients.[43] A number of the studies were carried out in cohorts of only patients with head injury and therefore do not support the concept that head injury is the unique component but rather could simply be a reflection of injury itself.[44,45] A cause-and-effect conclusion is, therefore, not confirmed epidemiologically in any of the English language studies to date.

NEW PARADIGM

We have factors that, though they may not be cause and effect, are associated with coagulopathy and we now have new epidemiological data that show early coagulopathy is independently associated with a poorer survival. Is there another causal model for abnormal coagulation after injury that could more adequately explain and incorporate these new findings? Could this new paradigm also explain the heterogeneity of incidence, severity, and outcome of posttraumatic coagulopathy? If coagulopathy appears early in certain patients, can we continue to assume the factors discussed in this article are the triggers or is it possible that they are just important potentates of an already-occurring abnormality in coagulation? Is it possible that coagulopathy after injury is a primary phenomenon that worsens the patient's outcome and is further worsened by the factors now considered to be the "causes"? The hypothesis generating retrospective studies needs to be confirmed with prospective studies and to ascertain if its occurrence in certain patients is associated with injury pattern, severity, timing, or another confounder.

If posttrauma coagulopathy is a primary phenomenon, further research needs to focus on what the inciting factor may be. It is possible that an innate patient-dependent variable, such as genotype, is associated with a "propensity to coagulopathy" after an injury and results in a change in the likelihood of survival? Just as the evidence is mounting that our genetic makeup not only determines the type of disease we may eventually get, there is evidence that it also determines how we respond to the treatment of that disease.

Researchers have shown that the effectiveness of chemotherapy may not be just related to tumor behavior and stage but also to the patient's genetic makeup. More specifically to coagulopathy, researchers from Duke University showed that post–cardiac surgery bleeding complications were associated with specific genetic expressions and that this was independent of the other known risk factors for postoperative bleeding in cardiac surgery.[46] Could it be that there is also a genetic makeup for the coagulation enzymatic cascade that is more vulnerable to disruption after an injury and that this varies across individuals? Consequently, after an injury, a subset of patients may be "hard wired" to continue to bleed despite adequate replacement strategies and respond more seriously to hypothermia, acidosis, and dilution. Resultantly, these patients are more likely to die of their injuries than an individual with a different genotype.

CONCLUSIONS

Coagulopathy and microvascular bleeding continue to be major contributors to early in-hospital death after an injury and new treatment approaches are needed to lessen this high mortality rate. Recent studies of early coagulopathy as a predictor of mortality provide a new hypothesis as to the explanation of the initiation of microvascular bleeding, where posttraumatic coagulopathy occurs earlier and is a primary, possibly patient-initiated, occurrence. This new paradigm considers posttrauma coagulopathy as a primary, rather than secondary, event after an injury.

A shift to this paradigm will increase the emphasis on earlier and more aggressive coagulation factor replacement to lessen hemorrhage-related mortality. As well, it could guide future research directions in the pursuit of new interventions to both identify those patients who will develop coagulopathy and the means by which to treat them.

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