A Clinical Review of Bleeding Dilemmas in Trauma

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Trauma is rapidly replacing stroke and cardiovascular disease as a leading cause of death in Western countries such as the United States, and almost a third (30%) of trauma deaths are due to blood loss. Although the new intervention strategies that have been developed and adopted by emergency care staff have reduced this mortality in recent years, bleeding continues to be a major challenge in the management of trauma patients. This paper reviews recent developments and controversies in trauma care, and, in particular, the potential role of procoagulant therapy using recombinant factor VIIa in the prevention of mortality due to bleeding.
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TRAUMA IS an increasingly common cause of death in civilian life, as well as a major cause of death during military action. In the United States, deaths due to trauma are rapidly overtaking the numbers who die from stroke and cardiovascular disease (*www.cdc.gov*). Road traffic accidents account for almost one third (15.0 per 100,000)[18] of the currently reported 147,000 (50.2 per 100,000) trauma deaths per year in the United States. Trauma is already the most common cause of death in young American adults[10] and, globally, young people between the ages of 15 and 44 years account for almost 50% of the world's injury-related deaths. In fact seven of the 15 leading causes of deaths for people aged 5 to 29 years are injury-related; these are road traffic injuries, suicide, homicide, war, drowning, poisoning, and burns.[22]

Almost one third (30%) of trauma deaths are due to blood loss.[16] Most of these deaths occur within the first 4 hours after injury.[1] Laceration or fracture of the scalp is the main cause of traumatic hemorrhage (occurring in 60% of cases); the remaining 40% are due to bleeding into the chest, abdomen, or retroperitoneum.[15] Management of massive bleeds through allogeneic transfusion is associated with immunosuppression[3,5] and an increased risk of infection,[8] which contribute to deaths occurring days or even weeks after injury.

A loss of 50% of blood volume without resuscitation is usually fatal and a hypotensive patient, who has lost 30% to 35% of blood volume and is in uncompensated shock, is close to death. The traditional approach to hemorrhagic shock has been to resuscitate patients aggressively to restore blood volume before surgical intervention. However, there are risks associated with resuscitation in addition to the potential delay to surgery, and such intervention is now the subject of controversy. Hence, trauma surgeons face the central dilemma of how best to limit blood loss and minimize the risks associated with fluid resuscitation. New interventions such as procoagulant therapy using recombinant factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) may have an important role in reducing bleeding following trauma in the future.

The Changing Role of Fluid Resuscitation

Until the 1990s, the standard intervention for hypotensive trauma patients was aggressive fluid resuscitation with the goal of restoring end-organ perfusion and oxygen delivery prior to surgery. Increase in circulating volume also increases cardiac output and blood pressure. However, it was suggested as early as 1920[6] that a sudden increase in blood pressure may prove detrimental since it has the potential to precipitate rebleeding from sites where physiological mechanisms have brought about cessation of hemorrhage. In addition, with the obvious exception of fresh-frozen plasma (FFP), most fluids administered to resuscitate the patient will also reduce blood viscosity and dilute clotting factors thus impairing hemostasis. Rethinking of aggressive fluid resuscitation followed the publication of the famous "Mattox trial" in 1994.[2] The investigators performed a prospective, single-center trial comparing immediate and delayed fluid resuscitation in 598 adults with penetrating torso injuries. All patients presenting had a pre-hospital systolic blood pressure of less than 90 mm Hg. A total of 203 of 289 patients (70%) who received delayed fluid resuscitation survived compared with 193 of 309 patients (62%) who received immediate fluid resuscitation ($P = .04$). The number of patients having one or more postsurgical complications was lower in the delayed fluid resuscitation group versus

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Table 1. Evacuation Times and Mortality Rates in Military Conflicts

Conflict Scene	Evacuation Times	Mortality
World War II	12-15 hours	3.3%
Korea	4-6 hours	2.4%
Vietnam	1-4 hours	1.8%

those receiving immediate fluid resuscitation: 23% versus 30%, respectively.

Numerous studies before and since this study have failed to demonstrate a survival benefit for aggressive fluid resuscitation before mechanical stabilization of the injury.[12,14] There is also evidence to suggest that restoring normal or near-normal blood pressure using fluid resuscitation before surgery may even worsen survival.[9,10,19,20] A recent Canadian prospective cohort study linked pre-hospital advanced life support with higher mortality rates than basic pre-hospital life support (29% *v* 18%, respectively). The authors concluded that in urban centers with highly specialized level I trauma centers, pre-hospital advanced life support was not beneficial to patients.[13]

Hence, medical personnel confronted with a hypovolemic trauma patient have to balance the administration of fluid, with its associated risks of rebleeding and increased blood loss, and withholding fluid; thereby allowing the possibility of immediate or rapid death from hypovolemia.

It is possible that avoiding fluid resuscitation completely, or at least delaying it until after surgery, can improve survival compared with the traditional aggressive approach. This strategy avoids both the risk of increased bleeding due to destabilized hematoma, and the delay incurred by resuscitation before surgical intervention. A relatively slow bleeding rate of 25 mL per minute would lead to death within 2 hours, while a steady blood loss of 100 mL per minute would be fatal within 30 minutes. The importance of rapid surgical intervention is supported by data from military conflicts showing a direct link between shortened evacuation times and improved survival (Table 1).[7]

With increasing numbers of studies showing no benefit for aggressive resuscitation before surgery, many trauma surgeons have adopted a strategy of targeted hypotensive resuscitation, although it remains controversial and is unsuitable for patients with head injury. This approach aims to achieve a blood pressure between 80 and 100 mm Hg, which is sufficient to maintain adequate perfusion for short periods while minimizing the risk of increased bleeding that can occur when large volumes of fluid are infused rapidly to achieve near-normal blood pressure.[21] Using this method, hypotensive resuscitation may also be achieved faster than complete normalization of blood pressure. There is evidence that primary hemostasis is re-established after 6 hours, and that patients who survive the first 6 hours following injury are, therefore, unlikely to die from hemorrhage.[17]

Potential Roles of Procoagulant Therapy

Although there are limited data on the use of rFVIIa in the acute management of trauma patients, procoagulant intervention offers some intriguing potential benefits. It appears likely that rFVIIa could potentially play an important future role in reducing fatalities due to hemorrhage following trauma. A hypotensive patient reaching hospital has already lost about a third of their blood volume and will die after losing about 800 mL more blood. Thus, any intervention that limits blood loss at an early stage may help prevent death. There are several potential uses for rFVIIa in trauma bleed management.

Immediate Intervention in the Field

rFVIIa administered in the field could promote stable hematoma formation in soft tissue and visceral injuries before the patient reaches the hospital. In addition, stabilizing clots at the accident site might protect patients from renewed bleeding following fluid resuscitation, allowing effective fluid replacement and reducing the risk of multiple organ failure.

Although this idea appears controversial today, there could be clear benefits of early procoagulant intervention for certain groups of patients, particularly those with a simple injury that requires little or no mechanical hemostasis (such as simple hemothorax or parenchymal injury to the liver, spleen, or kidney). Similarly, patients with predominantly venous bleeding from an injury such as a pelvic fracture may benefit from rFVIIa administered before mechanical intervention (such as laparotomy and external or internal fixation). Transient responders—patients whose blood pressure is temporarily restored before decreasing again after about 15 minutes—usually have a single vascular injury or single organ injury. This group is likely to require mechanical hemostasis. The role of rFVIIa in this group is less clear. For nonresponders to fluid resuscitation, who are usually suffering from massive parenchymal hemorrhage or large vessel injury, the priority should be to control their bleeding surgically without delay, and any presurgical intervention offers limited benefit.

Acute Head Injury

A particular challenge to treating clinicians is progression of injury due to continuing intracranial bleeding that places growing pressure on the brain

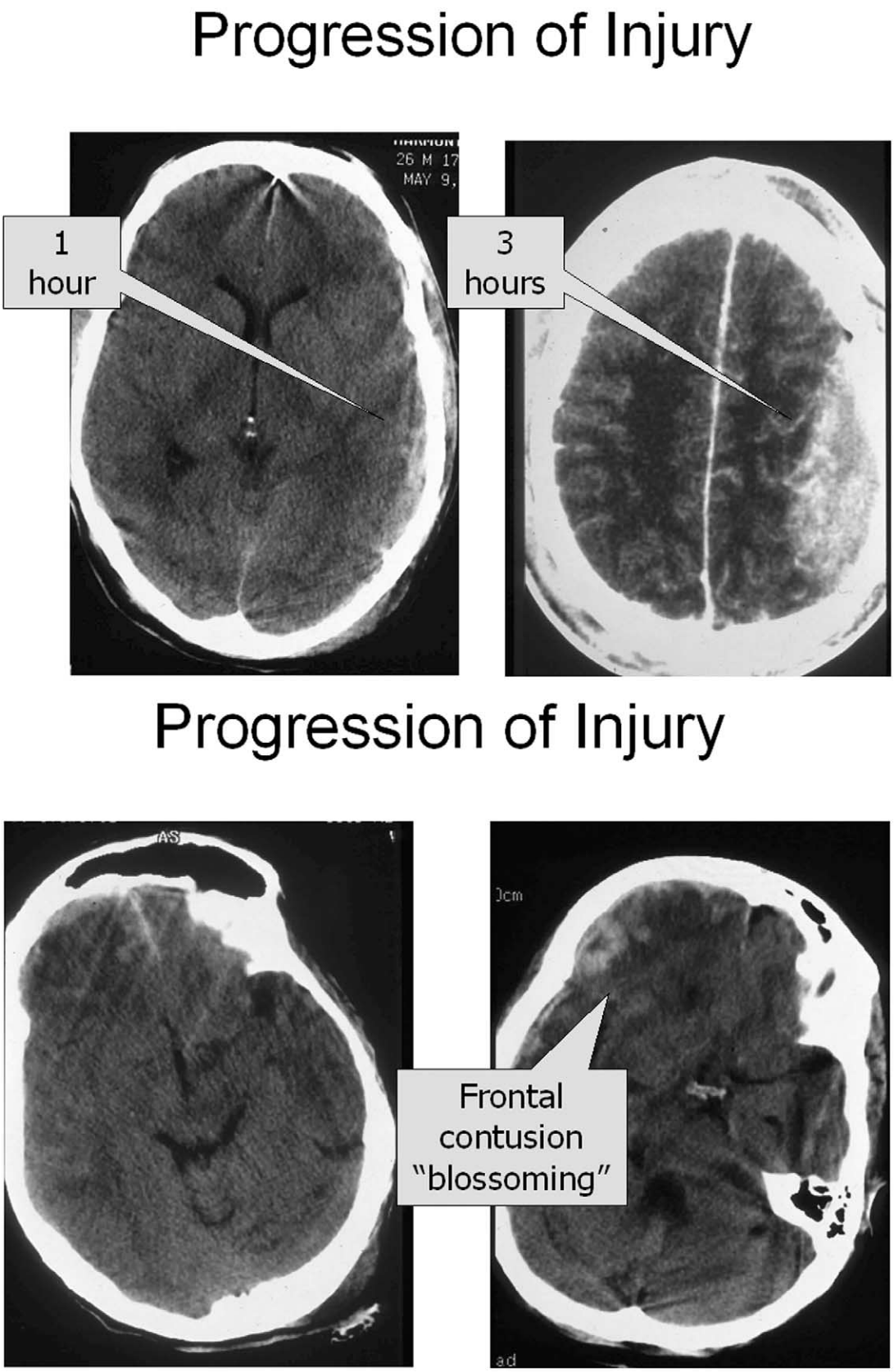

Figure 1. Progression of acute head injury. (Top) A young male patient who was admitted after falling off his skateboard. The first computed tomography (CT) scan was performed within 45 minutes of the injury being sustained, and shows a small epidural hematoma. In the second scan, performed 3 hours following the first scan, the epidural hematoma has increased. (Bottom) A patient with a temporal contusion; the second scan shows "blossoming" of the frontal contusion as the injury progresses over time. This type of injury might respond particularly well to intervention using rFVIIa.

following an intracranial injury. The potential for limiting this progression using procoagulant intervention is particularly exciting, as it offers an opportunity to protect patients from brain damage, as well as potentially reducing mortality following head injuries (Fig 1).

Consumptive Coagulopathy

Patients with consumptive coagulopathy remain a major challenge for trauma surgeons: even if surgical hemostasis is achieved, these patients continue to bleed. The so-called "death spiral"—characterized by hypothermia, consumptive coagulopathy, and acidosis—can resist all efforts at intervention and surgeons are currently ill-equipped to fight this condition. The death spiral is caused largely by hypothermia, which is a common problem following aggressive fluid resuscitation. Any hypotensive patient who receives 4 U of unwarmed crystalloid and 8 U of blood is likely to reach a core temperature below 35°C.

Most trauma surgeons follow an algorithm, typically giving platelet therapy first, followed by FFP, and then cryoprecipitate, while rewarming the patient. During the past 10 years, trauma surgeons have developed a "damage control" strategy to preempt the death spiral. This strategy involves cutting short surgery if a patient requires infusion of 10 U of blood, and performing temporary measures such as blood vessel shunts or bowel stapling with a plan to delay reconstruction. The patient is then resuscitated in the intensive care unit and given time to recover before surgery is completed, perhaps even the next day. Many have used rFVIIa in patients with consumptive coagulopathy, with impressive results.[11]

In a recent analysis of data on 210 patients who bled to death during the Vietnam War, we identified two new developments that might have reduced fatalities if they had been available at that time. These new developments were the damage control strategy to avoid consumptive coagulopathy, and the use of procoagulant therapy.[4]

Conclusions

- Targeted hypotensive resuscitation may offer better survival than aggressive fluid resuscitation.
- Maintaining stability of primary hemostasis at the site of injury that limits bleeding is an important consideration in the acute management of trauma patients.
- New interventions such as procoagulant therapy using rFVIIa are likely to become important elements in preventing mortality due to bleeding following trauma.
- Further trials are needed to explore the potential benefits of procoagulant intervention for trauma and traumatic brain injury patients.

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