REVIEW

Advances in resuscitative trauma care

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ABSTRACT

Over the last two decades, experimental and clinical data have begun to shape a more discriminating approach to intravascular (IV) fluid infusions in the resuscitation of trauma patients with presumed internal hemorrhage. This approach takes into account the presence of potentially uncontrollable hemorrhage (*e.g.*, deep intra-abdominal or intra-thoracic injury) versus a controllable source (*e.g.* distal extremity wound). This limitation on fluid resuscitation is particularly applicable in the case of patients with penetrating truncal injury being transported rapidly to a nearby definitive care center. Meanwhile, longstanding debates over the type of fluid that should be infused remain largely unresolved and further complicated by recent clinical trials that did not demonstrate support for either hemoglobin-based oxygen carriers or hypertonic saline. However, there is also growing evidence that does support the increased use of fresh frozen plasma as well as tourniquets, and intra-osseous devices. While a more discriminating approach to fluid infusions have evolved, it has also become clear that positive pressure ventilatory support should be limited in the face of potential severe hemorrhage due to the accompanying reductions in venous return. Controversies over prehospital endotracheal tube placement are confounded by this factor as well as the effects of paramedic deployment strategies and related skills usage. Beyond these traditional areas of focus, a number of very compelling clinical observations and an extensive body of experimental data has generated a very persuasive argument that intravenous estrogen and progesterone may be of value in trauma management, particularly severe traumatic brain injury and burns. *(Minerva Anestesiol 2011;77:993-1002)*

Key words: Resuscitation - Shock, hemorrhagic - Brain injuries - Burns -Estrogens - Ventilation.

The basic tenets of traditional trauma management prior to surgical intervention include direct control of obvious external bleeding, appropriate skeletal immobilization and assurance of an adequate airway and breathing.[1]

Furthermore, in cases of presumed internal bleeding within the skull, chest, abdomen, or pelvis (or other sites in which the hemorrhage cannot be externally controlled), rapid transport and transfer to a definitive care operative facility is paramount.[1-4] Beyond these basic tenets and therapies, intravascular access and fluid infusions have also been used routinely to help restore depleted intravascular volume.[1-5]

The problem is that many of these therapies may actually be harmful if not used or implemented appropriately. As trauma is not a generic process, the various presentations of trauma patients may determine the kind of therapies that should be provided.

Just as the term "cancer" is an umbrella word that describes a multitude of processes that require different interventions depending on the specific type of cancer, its anatomic location and its staging, so too trauma management is best determined by the basic mechanism of injury, its anatomic involvement and degree of physiological impact. In the following discussion, the "first do no harm" caveat will be explored and a

better delineation of the timing and degree of appropriate resuscitative interventions will be reviewed with current recommendations.

Restoration of intravascular volume

In addition to rapid transport for immediate surgical intervention, the traditional preoperative management of severely injured patients has been to take steps to ensure adequate organ perfusion. This approach generally has involved an attempt to normalize systolic blood pressure (SBP) by augmenting intravascular volume.[1, 3, 5-9] This parameter is measured routinely in the early phases of resuscitation because it is already an obligatory procedure for most patients and *severe* hemorrhagic states usually are associated with low SBP while other clinical signs of intravascular volume depletion and poor delivery of oxygen to various body tissues may be more ill-defined and less specific, particularly in the prehospital phase of resuscitation.[1, 3, 6]

While systemic arterial hypotension has become the most widely-used indicator for identifying potential shock states, it may not indicate the actual state of tissue oxygen perfusion. Some persons with adequate tissue perfusion may have a relatively low SBP, while those with a "normal" SBP may not always have adequate perfusion systemically. Recently, other parameters such as measuring base deficit and lactate levels, including point-of-care testing, have been used more and more to better predict those at greatest risk for development of end-organ damage and multiple-organ dysfunction syndrome.[10-15] In addition, technology such as near-infrared spectroscopy (NIRS) has been used to measure tissue oxygen saturation (StO_2) in peripheral musculature and these methods have correlated with base deficit prediction of poor outcomes or the need for massive transfusions.[14, 15] Nevertheless, such methodologies have not yet been routinely adopted and most are not even currently feasible for rapid use in the early phases of resuscitation such as the prehospital setting. Therefore, with the presumption that a low SBP may indicate a risk for shock states, attempts to elevate SBP have still remained a front-line therapeutic strategy for hypotensive trauma patients.

The intervention most often used to restore SBP towards "normal" levels has been the use of rapid intravenous (IV) infusions of an isotonic crystalloid (*e.g.*, normal saline, lactated Ringer's) or colloid (*e.g.*, albumin or hetastarch) solution.[2-6, 10] The original concept had its roots in several experimental studies from the 1950s and 1960s.[7, 8] Animals receiving both blood and IV isotonic fluid had a greater likelihood of survival after severe hemorrhage compared with no treatment or treatment with blood alone.[7, 8] Severe hemorrhage leads to a loss, not only of red blood cells, but intravascular volume as well resulting in a shifting (and loss) of extra-cellular fluids. In addition, hypoperfusion was presumed to cause further intracellular sequestration of the extravascular fluid that normally bathes the cells and facilitates the transfer of oxygen and other nutrients from the bloodstream to the tissues. Moreover, fractures, soft tissue trauma and other injuries can lead to edema formation that further depletes vascular space of fluid.

Although formal clinical trials had never been conducted to confirm the universal efficacy of this concept for all trauma patients, by the 1960's, IV fluid infusions empirically became the standard of care for major injury victims. What had not been taken into total account, however, was the consideration that most of the original experiments concerning fluids involved models of "controlled hemorrhage" in which bleeding (or blood removal) had been induced up to a certain point and then stopped.[7, 8] In other words, the models mimicked situations in which bleeding had been controlled. In contrast, many trauma patients may have on-going internal bleeding and this lack of control may present a different clinical circumstance.[3-5, 16-26] Growing evidence over the past two decades indicates that elevation of systemic blood pressure may be harmful prior to achieving adequate hemostasis.[16-29]

As opposed to the seminal controlled hemorrhage models that established the value of IV fluid resuscitation, more contemporary studies have begun to examine the effects of raising SBP during uncontrolled hemorrhage.[7, 8, 11-22] Among the various potential deleterious effects that may occur in this circumstance are the potential for increased blood loss and dilution of

clotting factors.[5, 16-18, 27] In turn, these complications can lead to increased mortality despite the original intention to improve perfusion.

These types of studies were summarized in 2003 in a systematic review that concluded "hypotensive resuscitation reduced the risk of death in all the trials investigating it".[26] As a quintessential example, Stern and colleagues demonstrated in a swine model of aortic laceration with severe hemorrhage, that there was far less mortality and no associated complications in vulnerable organs (both physiologically and histologically) among those animals who did not receive IV fluid infusions until surgical repair was conducted 75 minutes after the injury.[20] In contrast, the group receiving aggressive fluid infusions in the preoperative period fared much worse. As a result, current recommendations for fluid resuscitation call for assessments of both the mechanism and anatomical location of injury, as well as whether or not bleeding is likely controlled or ongoing.[2-6]

The concept that there is risk in raising SBP in the face of uncontrolled hemorrhage is neither new nor limited to trauma. Dating back to World War I, the premature elevation of SBP with fluid administration and even blood administration was described as harmful.[23] Deliberate tolerance of hypotension is also practiced in those with uncontrollable gastrointestinal or aortic aneursymal bleeding. Among the mechanisms believed to worsen outcomes are hydraulic and dilutional factors. For example, increasing blood pressure accelerates the rate of bleeding and can dislodge soft early clots, leading to increased (and more difficult to control) hemorrhage from vascular injuries.[16, 21, 27] Dilution of red blood cell mass by crystalloid or colloid infusion may further reduce oxygen delivery capacity despite the increased cardiac output. Dilution of clotting factor concentration may also lead to inhibition of clot formation.[9, 17] Finally, the resuscitative fluids themselves may have deleterious properties.[28, 29]

A large, prospective, controlled clinical trial was conducted in the late 1980's in which immediate preoperative IV fluid resuscitation was compared with fluid infusions that were delayed until arrival in the operating theater in patients presenting with SBP<90 mmHg following abdominal or thoracic penetrating (gunshot or stabbing) injuries.[24] The immediate fluid infusion group was provided liberal lactated Ringer's (LR) fluid resuscitation to reverse hypotension, but, similar to the experimental models, were found to have a higher mortality rate and a higher rate of postoperative complications compared with patients in the delayed resuscitation group. Similarly, in a prospective, randomized clinical trial examining hypotensive patients with both blunt and penetrating trauma, the patients were assigned to receive either fluid resuscitation targeted to maintain a SBP of either 80mmHg or less or to conventional care targeting a SBP>100 mmHg.[25] Although the overall mortality rate was identical, there were fewer complications and a shorter duration of hemorrhage observed in the lower SBP group. The authors of this study concluded that deliberate "hypotensive resuscitation" was not only well-tolerated by the patients, but it also led to earlier hemostasis.

It should be emphasized, however, that this approach should be applied only to patients with known or suspected uncontrolled bleeding. A hypotensive trauma patient with isolated severe hemorrhage emanating from an extremity will likely still benefit from immediate prehospital fluid resuscitation, provided the bleeding is promptly controlled with direct pressure or, as will be subsequently described, tourniquets, or topical hemostatic agents.[1-5] On the other hand, controversies still remain, particularly in the case of patients with multi-system blunt injury and especially those with severe closed head injury.

Blunt *versus* penetrating injury

Most of the laboratory data supporting deliberate hypotension comes from models of discrete arterial hemorrhage. Accordingly, the large human trial from Houston enrolled only patients with penetrating thoracoabdominal trauma, and the most significant results were observed in cases in which distinct vascular injuries were the main source of hemorrhage.[16, 24] Studies have not fully addressed the more complicated issue of blunt trauma, often characterized by numerous sites of hemorrhage and substantially greater

direct tissue injury overall and greater extravascular sequestration of free fluid. Blunt trauma is also likely to include some degree of traumatic brain injury (TBI), which is thought to be exquisitely sensitive to episodes of hypotension.[2, 5, 9] In such cases, the rationale for IV fluid infusions is much stronger and they continue to be recommended by most practitioners for such circumstances.[1]

At the same time, as indicated previously, patients with polytrauma can also have distinct vascular injuries that are subject to some of the same concerns held for those with penetrating injuries.[25] Creation of a secondary bleed may also worsen the outcome, even with severe head injuries.[16, 21, 22] The preponderance of evidence suggests that achieving primary hemostasis is the most important goal of resuscitation, regardless of mechanism of injury, and that deliberate hypotension may still be beneficial while bleeding is uncontrolled, regardless of the mechanism.

In the laboratory, there have been a number of trials of deliberate hypotension in the treatment of combined hemorrhage and TBI. Stern *et al.* showed that animals fared better with a more controlled fluid infusion approach.[22] Moreover, Stern *et al.* have demonstrated that a slow infusion, not a rapid bolus approach, may be superior in the case of near-fatal hemorrhage models.[21] In essence**,** how fast the fluid is delivered is of greater concern than simply the restriction of fluid administration. Delayed and slower infusions may be less apt to accelerate on-going hemorrhage or to cause rebleeding. This construct is consistent with the notion that soft clots may not tolerate higher pressures until fibrin deposition occurs, a process thought to occur about a half hour into the clotting process.[21] Therefore, future research initiatives should not only stratify patients with blunt trauma and those with severe head injury, but also the timing and rate of fluid infusions.

Fluid resuscitation in extremis

Despite the recognized detrimental effects of aggressive fluid resuscitation in uncontrolled hemorrhage, many animal studies have also suggested that blood or fluid administration may be of value in patients with extremely "severe circulatory compromise" such as a mean arterial pressure less than 40 mmHg. Patients with such a degree of hypotension typically present without a measurable blood pressure and are usually unconscious. Considering the grim outlook for these patients, rapid fluid infusion might be empirically reasonable. In practice, few patients survive when there is a prehospital loss of pulse and the survivors are usually those patients with anatomically discrete injuries (airway obstruction, tension pneumothorax, cardiac tamponade, single vessel hemorrhage) in whom rapid resuscitation is combined with equally rapid control of the underlying etiology.[30]

Another consideration for patients in extremis is to consider deficiency of endogenous vasoactive mediators and to consider the infusion of vasopressor agents such as arginine vasopressin or terlipressin.[31-33] While these types of interventions have not yet been explicitly embraced, preliminary experimental and clinical data have been very compelling, at least for select groups of patients. Nevertheless, such potential benefits of induced vasoconstriction in terms of promoting hemostasis and augmenting cerebral perfusion pressure must also be balanced with the resulting possible detrimental effects of increasing blood pressure in cases of uncontrolled hemorrhage as well as any possible long term effects of prolonged local ischemia in certain constricted tissue beds.

Alternative resuscitation fluids

On-going controversies over the use of colloid solutions versus crystalloid infusions as well the use of hypertonic compounds have complicated the assessment of fluid resuscitation regimens for years.[2-4, 6] Hypertonic saline (HS) solutions permit a so-called "small volume" resuscitation, with the observation that additional bleeding with this type of solution (HS) is not as bad as with isotonic solutions for the degree of SBP elevation.[16, 21] Also, HS has been shown experimentally to have anti-inflammatory properties and anti-edema effects in TBI.[2, 29] Nevertheless, several recently-completed trials, including

a large multi-center trial of HS in hypotensive trauma patients and those with TBI, sponsored by the U.S. *National Institutes of Health* (NIH), did not demonstrate any improvements in outcomes.[34, 35]

Regardless of the fluid of choice, HS or saline, colloids or lactated Ringer's, these fluids do not carry oxygen, the main concern in terms of reperfusion of tissues. In contrast, hemoglobin-based oxygen carriers (HBOCs) have the possibility to improve the dynamics of early resuscitation. One of the latest compounds, HBOC-201 (Hempure™, Biopure, Inc,) derived from bovine sources, has shown benefit, when combined with deliberate hypotension, in several animal studies.[36, 37] However, HBOC-201, like many other HBOCs have nitric-oxide scavenging effects that lead to smooth-muscle constriction and subsequent blood pressure elevation.

At present, it is not known if the oxygen delivery properties of these agents will outweigh the risk of secondary hemorrhage. One multicenter trial of a human-blood based HBOC (Polyheme™, Northfield Inc.) was completed in multiple centers using a broad population of trauma patients, not just those with severe hemorrhagic states. No improvement in survival was demonstrated and there were concerns that the compound carried an increased, though very low, incidence of adverse cardiovascular events.[37] Despite a lack of convincing human evidence at this time, the concept of providing improved oxygen transport in the face of uncontrollable hemorrhage is of paramount concern to trauma resuscitation. Therefore, investigators still strongly support the development and future clinical trials of HBOCs or similar technologies.

Non-surgical hemostasis as an intervention

Some evolving therapies with the potential to impact trauma resuscitation include the use of both topical and systemic hemostatic agents to more rapidly control bleeding.[38-41] If definitive hemostasis can be achieved in the prehospital environment then the interval in which deliberate hypotension is of benefit may be reduced or eliminated.

A number of organic compounds (*e.g.*, chitosan, zeolite crystals) have been found to facilitate coagulation in open wounds, and have been packaged for external use in trauma patients and battlefield injuries.[38] These compounds are associated with some expense and the consensus is to use them in relatively deep wounds with significant bleeding when simple gauze and pressure dressings appear to be fully adequate. Based on the preliminary data, evolving generations of these products may be cheaper and even more effective.

In addition to topical products, certain systemic interventions also provide some promise, helping to further support the concept of "non-surgical" hemostasis.[2, 40, 41] Accordingly, the use of recombinant human coagulation factor VIIa has been reported to be beneficial in hospitalized trauma patients, both in military and civilian settings.[42-46] For example, in retrospective review of military experience, early use of the factor VIIa reduced blood utilization by 20%. However, more recently, in the civilian setting, the effectiveness of recombinant Factor VIIa (rFVIIa) was not borne out after a prospective trial in which a survival advantage could not be demonstrated.[45] It still has been considered for "off-label" use and it is generally suggested only after failure of standard surgical and embolization techniques with an appropriate transfusion treatment.[46] In essence, this would obviate its use in the early resuscitative phases of trauma.

Another ongoing international research effort has involved the use of the anti-fibrinolytic tranexamic acid in trauma patients. The recently published CRASH-2 Trial provided compelling data that supported its use, but this has not yet been widely adopted to date.[47] Other considerations for intravascular hemostatic agents include fibrinongen which is best seen as an adjunct "drug" that could be added to other coagulation factors as well as prothrombin which has been considered as a possible substitute for fresh frozen plasma.[48-52]

In terms of fresh frozen plasma, observations by the U.S. military during the Iraq experience indicated a mortality-reducing effect when the addition of higher proportions of fresh frozen plasma (FFP) infusions were provided for every unit of red blood cells transfused.[53] In a

retrospective review of severe post-traumatic hemorrhage cases involving more than 10 units of transfusion in a 24 hour period, the use of a 1:1.4 ratio of FFP to blood was far superior to 1:2.5 and 1:8 ratios. Specifically, the overall mortality rates were 19%, 34%, and 65%, respectively (P<0.001) and the hemorrhage mortality rates were 37%, 78%, and 92.5%, respectively, (P<0.001). Despite the potential for "survival bias" in these retrospective studies, recent experience in the U.S. civilian setting has indicated the decreased need for transfusions.[2, 3, 54-56] These data suggest a stronger role for early use of plasma in massive transfusion circumstances, but larger controlled trials will likely be recommended and encouraged to validate these findings.[2, 3]

Beyond chemical hemostasis, mechanical mechanisms appear to be very effective in extremity trauma. Recent experience from the US military in Iraq has documented the relative safety and efficacy of tourniquets.[57] In several hundred applications ranging from 15 minutes to two hours in duration, complications were rare. No amputations resulted from their use, only those secondary to primary wounds. The only other observed complications were 10 neuropraxias, six related to the primary wound, and just four secondary to the tourniquets. Of the ten total neuropraxia cases, however, all eventually resolved themselves or were resolving at the time of data acquisition. In all ten cases, application of the tourniquet was judged to be life-saving.[57]

Another attractive therapy proposed for early resuscitation from hemorrhagic shock is the use of induced mild hypothermia.[58] Induction of decreased core temperature has been associated with improved survival from hemorrhage in a number of animal models.[58] However, this technique has never been tested in human trauma patients because of historical concern for complications with associated incidental (not induced) hypothermia, such as worsening coagulopathy, increased incidence of sepsis, and the metabolic consequences of re-warming and reperfusion. Therefore, at the current time, induced hypothermia remains a theoretical intervention that still warrants further studies.

Positive pressure ventilation can be detrimental in trauma

While "airway, breathing and circulation" has been a traditional mantra of resuscitation, inappropriate use of positive pressure ventilation (PPV) may be profoundly detrimental.[13, 59-62] Although prehospital endotracheal intubation by emergency medical services (EMS) personnel has received significant criticism in recent years, it is not the procedure itself, but the factors surrounding it that shape its success in saving lives or it role in being detrimental to patient care.[60, 61] In addition to advanced airway skills performance being enhanced by EMS deployment strategies that optimize experience and advanced procedure utilization, a focus on ventilatory management is critical to optimizing outcomes.[60-62] In many EMS systems that have had enjoyed high survival rates for trauma, and particularly in cases of post-traumatic circulatory arrest, a focus on very controlled (limited) delivery of PPV has been associated with improved outcomes.[30] In essence, "ventilation should match perfusion" and in low flow states with diminished cardiac pre-load, the need for ventilation is minimized and the deleterious effect of PPV on inhibiting venous return is exponentially exaggerated in severe trauma with intravascular volume depletion.[60, 62] Furthermore, controlled ventilatory support can actually improve cerebral perfusion.[13] In some jurisdictions where individual paramedic experience is diluted by competition for skills usage because the EMS system has many paramedics, endotracheal intubation might be eliminated from the protocol. In others, where paramedics are kept relatively busy because of deployment strategies, successful placement of the tube will be better ensured and accompanying education in controlled ventilatory rates will prevent unnecessary deaths.[61]

Changing patterns in intravascular access

One other intervention that is worth mentioning is the increasing use of intra-osseous devices for trauma. With more effective designs, many prehospital care systems are using new intra-osseous devices as first line therapy for non-

traumatic cardiac arrest and induction of therapeutic hypothermia models.[63, 64] The EZ-IO device (Vidacare, Inc) is now being used by most paramedic programs and has been approved for both humeral and tibial injection sites as well as pediatric use and many prehospital care agencies are also using the device as alternate device for trauma resuscitation. In contrast, the U.S. military in Iraq has exclusively used the The F.A.S.T.1™ System (Pyng Medical Corporation), a sternal intra-osseous device as first-line intervention for intravascular access. No studies have demonstrated a life-saving advantage other than an inferential observation of providing earlier intravascular access.[63, 64]

The evolving role of sex hormones in trauma

Numerous recent studies have indicated differences between men and women, and even those in adolescence, in terms of their respective physiological responses to critical illness and injury as well as their relative rates of survival and recovery in post-traumatic circumstances.[65-69] As a result, the potential strong influence of sex hormones such as estrogen and progesterone have gained significant attention in trauma care.[65-69] Some studies also have indicated that estrogen may also provide advantages even in pediatric trauma.[67]

Estrogen, in particular, may have protective effects in numerous conditions ranging from global ischemic insults and massive systemic inflammatory responses to devastating focal injury and apoptosis in vital organs.[65, 67-74] Furthermore, an exogenous infusion of estrogen may not only have a direct therapeutic benefit in some instances, estrogen administration may also be synergistic with other resuscitative interventions.[65] A significant body of laboratory evidence, bridging across a variety of species and a breadth of experimental models, now supports the concept that estrogen may be an effective therapeutic intervention for a spectrum of severe physiological insults and injuries.[65-74, 76]

Although definitive clinical trials are still lacking, the striking experimental evidence, as well as several compelling clinical observations have begun to generate a very convincing argument that IV estrogen, and perhaps other female sex hormones such as progesterone should be administered immediately and routinely to all critically injured persons.[65, 75] What makes this provocative argument even more persuasive is the longstanding, documented safety and simplicity of a single dose of IV estrogen administration for various illnesses and conditions over the past several decades as well as the relatively inexpensive cost of treatment.[65]

Specifically in terms of traumatic injury, evolving information has indicated the protective attributes of estrogen in the case of patients presenting with severe TBI.[65, 69] Normally, estradiol levels in the cerebrospinal fluid (CSF) of young men is about one-tenth the level of that found in the bloodstream. However, unusually high estradiol (estrogen) levels have been measured in the CSF of men with severe TBI who were later found to have good outcomes.[65, 69] In fact, a CSF to serum ratio >1 was found to be the cut-off point that was predictive of a good outcome [69] *versus* a poor outcome when the CSF levels remained lower than the serum. The teleological inference here is that the brain protects itself by secreting (or sequestering) high levels of estrogen and that a high level of CSF estradiol is related to an improved outcome. A recent experimental study attributed the mechanism to be increased aromatase expression and thus an increased production in response to the insult.[77]

While there are numerous pathways through which estrogen attenuates cellular injury and the response to injury, there are two basic principles that should be emphasized. First, the effects of sex hormones are neither cell-type nor insult specific. It appears that estrogen has many of its effects within the mitochondria of every cell in the body. It does so by sustaining the activity of cells that might have otherwise become apoptotic, down-regulated and damaged by oxidant-type injury.[65] For example, this universal effect was demonstrated in recent laboratory studies of severe torso burns.[73, 74] Despite its "remote" anatomic location distant from the injury site, severe inflammatory effects can be found in the brain soon after severe torso burns. This is presumably a part of a systemic inflammatory response.[73] Nevertheless, that inflammatory response in an

organ not intuitively associated with estrogen actions can be prevented by early estrogen administration.[73, 74] Among other markers, serum levels of interleukin-6 (IL-6), the strongest indicator of poor outcomes in burns, rise rapidly in remote organs after the initial insult. However, those remote elevations are specifically blocked by estrogen.[65, 72, 74]

Beyond the therapeutic potential, both estrogen and progesterone are relatively inexpensive, especially when compared with the typical cost of an intensive care unit hospitalization.[65] Also, when considering its application, these drugs might be used in tens of thousands of persons a day worldwide. Even if affecting a small percentage of cases, they may not only be life-saving, but they may very well improve the recovery for thousands of injured persons globally each day.[65]

Progesterone has been the subject of clinical investigations and it has been shown to provide benefits, particularly in TBI.[65, 70, 75] In a preliminary safety and clinical feasibility study of progesterone for TBI, there were dramatic improvements in 30-day survival [75] with its administration. This dramatic clinical effect was demonstrated despite the fact that, in some cases, the hormone was not administered for many hours after injury onset.[75] While the primary effect of progesterone has been attributed experimentally to decrease in brain edema, the mechanistic pathways appear to be distinct from estrogen, thus providing a possible additive or even synergistic effect.[70] At the current time, it appears that resuscitative endocrinology will become more and more of a major focus for trauma investigators.[65, 76]

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Conflicts of interest.—The authors do not have any financial conflicts of interest with regard to the material discussed except that they are funded by the National Institutes of Health for conducting studies in this area of interest. The article does suggest "off-label" uses of estrogen, but the U.S. Food and Drug Administration (FDA) has approved several Investigational New Drug (IND) applications made by the authors to formally study the use of estrogen in the conditions mentioned in this text

Received on February 2, 2011 - Accepted for publication on June 16, 2011.

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