

PERSPECTIVE

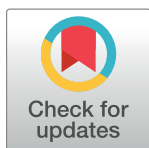
Trauma care: Finding a better way

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“There’s a way to do it better—find it.”—Thomas Edison (1847–1931)



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Abbreviations: EPR, emergency preservation and resuscitation; FFP, fresh frozen plasma; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDACI, histone deacetylase inhibitor; HS, hemorrhagic shock; TBI, traumatic brain injury; VPA, valproic acid.

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Changing patterns of deaths due to injuries

Since the second half of the 20th century, we have seen revolutionary changes in medicine, and trauma care is no exception. Injuries remain the primary cause of death for Americans under 46 years of age [1], but the patterns are changing. Today, in massively bleeding patients without head injuries, mortality beyond the first 24 hours is under 10% [2]. Unfortunately, the area in which we have failed to make a difference is the period immediately following the injury, including the prehospital phase. The majority of deaths in this period are due to hemorrhage and/or traumatic brain injury (TBI). Bleeding is the more treatable of these 2 causes of death, which makes it the number 1 cause of preventable deaths. Despite numerous advances in trauma care, a recent multinational trial of more than 20,000 patients [3] demonstrated that most deaths occur within a few hours of injury, with <2.5% of the injured succumbing to multiple organ failure. Similarly, in combat, 87% of battlefield deaths occur before reaching a medical facility [4]; nearly a quarter of these injuries are considered potentially survivable, and this category is largely (91%) made up of deaths due to bleeding. Thus, the current goal of early care is to keep patients alive long enough to be evacuated to higher echelons of care for definitive treatment.

Future directions

In the not-too-distant future, trauma care is likely to be very different from the current practice. In addition to early hemorrhage control and damage control resuscitation, we are also likely to see the following:

- The emergence of specific prosurvival drugs that can be given in the prehospital setting to keep injured people alive long enough to permit transfer to higher levels of care.
- Early (prehospital) use of preserved plasma products, platelets, and red blood cells.
- Availability of blood “farming” to eliminate the logistical barriers to supply, in which immortalized cell lines could efficiently generate red blood cells, in vitro, in a sustainable fashion [5].
- Development of safe and effective nonblood oxygen-carrying fluids that can be easily administered.

- Temporary use of hypothermia or hibernation strategies for patients with potentially survivable injuries but who need more time for surgery or transfer.
- Individualized therapy, also known as precision medicine, with administration of agents based upon the individual's specific needs.
- Monitoring of response to therapy that goes beyond the measurement of basic physiology by looking at key molecular and cellular disturbances.

Many of these novel treatments are already at the cusp of clinical reality, and I discuss 2 examples here.

Pharmacological treatment to create a prosurvival phenotype

We know that shock can disrupt cellular acetylation homeostasis by altering the balance between the histone deacetylase (HDAC) and histone acetyltransferase (HAT) families of enzymes [6]. Valproic acid (VPA), a commonly used anti-seizure medicine, is a nonselective histone deacetylase inhibitor (HDACI) when given in larger doses (higher than the commonly used anti-seizure dose) and can cause rapid and reversible acetylation of numerous nuclear and cytoplasmic proteins to create an anti-inflammatory and prosurvival phenotype [6,7]. In fact, a single dose of VPA, even in the absence of conventional resuscitation strategies, has been shown to improve survival and mitigate organ damage in models of lethal hemorrhage [8], poly-trauma [9,10], septic shock [11], ischemia-reperfusion injury [12], and TBI [13]. Using a variety of in vitro and in vivo models, we have also identified multiple molecular pathways that are modulated by VPA treatment [6,7]. These findings are potentially clinically relevant, as we have shown that expression profiles of various HDACs in circulating cells are associated with differences in clinical outcomes in trauma patients [14]. Additionally, tissues obtained from trauma patients display decreased acetylation, which can be rapidly normalized (ex vivo) with HDACI treatment [15].

These promising preclinical results have allowed us to perform a Phase I clinical trial of VPA for the treatment of hemorrhage (ClinicalTrials.gov, NCT01951560), and Phase II and III clinical trials are expected to follow. This pharmacological approach is equally effective when hemorrhage is complicated by severe TBI. Working with clinically relevant large-animal models of TBI and hemorrhagic shock (HS), we have shown that a single dose of VPA can attenuate brain lesion size, inflammation, and edema within 6 hours of treatment [16]. Treatment with fresh frozen plasma (FFP) has also been shown to be very effective, both as a monotherapy [17] and in combination with VPA—resulting in a synergistic effect [18]. VPA treatment up-regulates expression of beneficial genes in the injured brain [19,20], modulates posttraumatic brain metabolism [21], and improves long-term neurological recovery and healing [22] in clinically relevant models of TBI combined with HS.

In large animals, a single dose of VPA (150 mg/kg) restores acetylation and attenuates cell death, as evidenced by smaller brain lesion size and edema [22]. In the Phase I VPA trial, we found that doses of 130 mg/kg and 140 mg/kg were well tolerated in humans with no dose-limiting toxicities [23], and high-throughput proteomic analysis (in the 120 mg/kg cohort) has revealed 140 unique differentially expressed protein domains [24]. VPA also reversibly alters nucleosome topography [25] and activates neurogenic transcriptional programs in the adult human brain following traumatic injury [26]. The fact that VPA has been in clinical use for >40 years, is relatively inexpensive (approximately \$40 per dose), has no special storage needs, and is easy to administer justifies its development as a “bridge therapy” for austere field care environments.

Therapeutic hypothermia

Often, the underlying injuries are repairable, but a patient dies of irreversible shock or severe brain damage. In this setting, strategies to maintain cerebral and cardiac viability long enough to gain control of hemorrhage and restore intravascular volume could be lifesaving. This requires an entirely new approach to the problem, with emphasis on rapid total body preservation, repair of injuries during metabolic arrest, and controlled resuscitation, the process of which has been termed emergency preservation and resuscitation (EPR). Currently, hypothermia is the most effective method for preserving cellular viability during prolonged periods of ischemia [27]. It is clear from canine models that rapid induction of deep/profound hypothermia ($<15^{\circ}\text{C}$) can improve an otherwise dismal outcome after exsanguinating cardiac arrest [28,29]. Our team has used clinically realistic large-animal models of lethal vascular injuries and soft tissue trauma to demonstrate that profound hypothermia can be induced through an emergency thoracotomy approach for total body protection, with excellent long-term survival and no neurological damage or significant organ dysfunction, and that otherwise lethal vascular injuries, above and below the diaphragm, can be repaired under hypothermic arrest with greater than 75% long-term survival [30].

Subsequent studies have determined that, to achieve the best results, profound hypothermia must be induced rapidly ($2^{\circ}\text{C}/\text{min}$) and reversed at a slower rate ($0.5^{\circ}\text{C}/\text{min}$) [31,32]. The optimal depth of hypothermia is 10°C , and decreasing the temperature to ultraprofound levels (5°C) may worsen the outcome [33]. If hypothermia is induced appropriately, the safe duration of total body preservation is around 60 minutes [34], and there is no increase in postoperative bleeding or septic complications in the setting of solid organs and bowel injuries [35]. This approach may have significant implications not only for treating traumatic injuries but also for preserving organs for transplant [36]. The expertise to preserve the viability of key organs during repair of otherwise lethal injuries is now clearly available [27]. Although there are logistical challenges to the adoption of EPR in trauma practice [37], a prospective multi-institutional trial is already underway to establish its feasibility [38].

Discussion

To save the numerous lives that are lost to hemorrhage and TBI every day, new therapeutic approaches are needed. There is clearly room for improvement. According to the United States Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, about a quarter (27 million in 2013) of all emergency department visits are due to injuries [39], resulting in 3 million hospitalizations and nearly 193,000 deaths—1 person every 3 minutes [40]. As opposed to cancer, cardiovascular disease, and stroke, injuries disproportionately strike people in the prime of their lives. In fact, 59% of all deaths among people 1–44 years of age in the US are due to injuries, which is a higher proportion than all noncommunicable and infectious diseases combined. In 2013, the total cost of injuries in the US was estimated to be \$671 billion [41,42]. Globally, according to the World Health Organization, injuries kill more than 5 million people each year, which is nearly 1.7 times the number of fatalities from malaria, tuberculosis, and HIV combined [43]. Many resource-constrained countries lack established trauma systems resulting in prolonged prehospital times, and the healthcare facilities lack resources that are taken for granted in resource-rich countries (e.g., well-stocked blood banks, intensive care units, advanced radiology, sophisticated monitoring tools). Arguably, easy-to-administer, cost-effective pharmacological interventions are logistically a much more attractive option in these resource-constrained settings, as we have already seen with tranexamic acid in the CRASH-2 trial [3]. Similarly, the battlefield environment is another place where rugged, easy-to-use interventions that can keep an injured person alive long enough to get

evacuated to specialized care can save numerous lives. Many such technologies are potentially within our grasp; we just need to be open to change.

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