ICU MANAGEMENT & PRACTICE

ICU Volume 13 - Issue 4 - Winter 2013/2014 - Matrix Features

Therapeutic Hypothermia in Severe Trauma (Samuel A. Tisherman)

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Uncontrolled, exposure hypothermia is associated with worse outcomes in trauma patients. In contrast, laboratory studies suggest benefit of controlled, therapeutic hypothermia for haemorrhagic shock, traumatic cardiac arrest, traumatic brain injury and spinal cord injury. Well-designed, prospective studies are needed.

Introduction

Spontaneous, uncontrolled hypothermia occurs in many victims of major trauma. Shock, alcohol and drug intoxication, sedation, and anaesthesia limit the ability of trauma patients to maintain normal temperature homeostasis. Exposure for evaluation and operative interventions can increase heat loss. Cooling is further exacerbated by the administration of room temperature intravenous fluids and blood products. In the end, hypothermia may just represent the result of energy depletion from shock. The more severe the injury, the greater the risk of hypothermia (Gregory et al. 1991).

Several studies have demonstrated a strong association between the development of hypothermia and mortality in trauma patients (Jurkovich et al. 1987; Luna et al. 1987). Since the development of hypothermia is multifactorial and many of these factors may directly increase mortality, it has been difficult to clearly define the independent impact of uncontrolled hypothermia on trauma outcomes. Utilising a large state-wide trauma database, Wang et al. (2005) demonstrated an independent association between the development of hypothermia and mortality, controlling for age; sex; injury severity score; head, abdominal, and skin abbreviated injury scale; systolic blood pressure; mechanism of injury; intravenous fluids; and route of temperature measurement. All of these factors were independent predictors of hypothermia. The adjusted odds ratio for death in patients who became hypothermic (≤35ºC) was 4.04 (95% CI: 3.34–4.89). Similarly, the odds ratio for death in patients with isolated traumatic brain injury who became hypothermic was 3.14 (CI: 2.12–4.67).

Based upon the current clinical literature, the standard of care for severely injured patients remains active rewarming to maintain normothermia. Consideration for therapeutic hypothermia is challenging for investigators because of this current dogma.

Haemorrhagic Shock

Therapeutic, controlled, mild hypothermia (32-34ºC) has been studied in laboratory experiments using haemorrhagic shock models, with or without significant tissue trauma. Hypothermia has beneficial effects on the heart, liver, and skeletal muscle. More importantly, hypothermia consistently improves survival (Wu et al. 2005; George et al. 2010). For example, using a porcine model of prolonged haemorrhagic shock and trauma with intensive care life support throughout, Wu et al. (2005) demonstrated improved 24-hour survival.

Why is there such a dichotomy between the beneficial effects of hypothermia demonstrated in the laboratory and

the strong clinical association between hypothermia and worse outcomes in patients? First, and perhaps most important, is the physiologic difference between uncontrolled, exposure hypothermia in patients, which can be associated with energy depletion, shivering and catecholamine

responses, as compared to controlled, therapeutic hypothermia, during which shivering and stress can be prevented with sedation. Second, coagulopathy may play a role, though coagulation studies at 34ºC and experience with therapeutic hypothermia after cardiac arrest or traumatic brain injury do not suggest clinically relevant coagulation abnormalities at this temperature (Resnick et al. 1994; Watts et al. 1998). Third, it is possible that the amount of tissue trauma commonly seen in trauma patients may not be well replicated in the laboratory. Fourth, patients receive allogeneic, banked blood, while animal models typically include reinfusion of fresh, autologous blood.

No prospective, randomised trials of therapeutic hypothermia have been conducted in trauma patients. The only prospective, randomised trial related to temperature management in trauma patients compared standard rewarming with a novel continuous arteriovenous rewarming technique in a small number of patients who were already hypothermic (Gentilello et al. 1992). There was a suggestion of short-term (but not long-term) survival benefit with faster rewarming.

As mild, therapeutic hypothermia during severe haemorrhagic shock may delay or prevent cardiac arrest and may improve survival, a randomised clinical trial seems warranted.

Cardiac Arrest

Mild hypothermia has become standard therapy for comatose patients after non-traumatic cardiac arrest. Recommendations from the American Heart Association suggest that patients who remain comatose after resuscitation from an out-of-hospital cardiac arrest caused by ventricular tachycardia/fibrillation should be cooled to 32-34ºC for 12-24 hrs (Peberdy et al. 2010). They further suggest that there may be benefit of therapeutic hypothermia after in-hospital cardiac arrest and after cardiac arrest from other causes, possibly including trauma. For comatose trauma patients, without traumatic brain injury, who have suffered a cardiac arrest, therapeutic hypothermia should be considered if there is no clear contraindication, such as coagulopathy (Tuma et al. 2011).

For patients who exsanguinate from trauma, surgeons have little time to obtain haemostasis and adequately resuscitate patients before cardiac arrest is irreversible. Typically, these patients undergo emergency department thoracotomy, but survival is less than 10% (Rhee et al. 2000). Emergency Preservation and Resuscitation (EPR) has been developed as a novel approach to managing such patients by rapidly cooling them to allow tolerance of a prolonged period of circulatory arrest, during which haemostasis is achieved, followed by delayed resuscitation using cardiopulmonary bypass (CPB) (Tisherman 2004).

For induction of hypothermia (10-15ºC) for EPR, the fastest methods seem to be either a flush of cold saline directly into the aorta (Tisherman 2004) or use of a CPB circuit with ongoing low flow (Sailhamer et al. 2007). Delayed resuscitation then requires full CPB. The longer the period of hypothermic circulatory arrest that is desired, the deeper the level of hypothermia that is required. Profound hypothermia (10ºC) with glucose and oxygen in the flush can allow good neurologic recovery after even up to 3 hours of circulatory arrest (Wu et al. 2008). The optimal fluids and drugs for EPR still need to be developed. Clinically relevant dog and swine models with complex injuries have demonstrated that EPR has the potential to allow injury repair and neurologically-intact survival (Wu et al. 2006; Sailhamer et al. 2007).

Based on the preclinical studies, investigators at the University of Pittsburgh have developed the EPR for Cardiac Arrest from Trauma (EPR-CAT) feasibility trial (University of Pittsburgh). The study will enrol victims of penetrating trauma who suffer a cardiac arrest within 5 minutes of arrival at the trauma centre, but do not respond to initial resuscitation, including emergency department thoracotomy. The aorta will be cannulated with an arterial CPB cannula to enable rapid flush of ice-cold saline until tympanic membrane temperature is less than 15ºC. At that point, the patient can be rapidly transported to the operating room for resuscitative, damage-control surgery and delayed resuscitation with CPB. The protocol will require a coordinated effort by emergency physicians, trauma and cardiac surgeons, perfusionists, anaesthesiologists and operating room staff trained in the EPR technique. The primary outcome variable will be survival to hospital discharge without major neurologic disability. As the study progresses, the criteria and the technique may be revised.

Traumatic Brain Injury

Laboratory studies have demonstrated that early induction of mild to moderate hypothermia can improve many physiologic parameters, particularly intracranial pressure, and outcome after traumatic brain injury (TBI). Clinically, one single-centre randomised, controlled trial of early, post-TBI hypothermia (33ºC for 24 hours) demonstrated benefit at 6 months, but not 12 months, in a subset of patients with initial Glasgow Coma Scale (GCS) of 5 to 7 (Marion et al. 1997). The first, multi-centre North American Brain Injury Study: Hypothermia (NABIS:H) failed to demonstrate benefit of hypothermia at 33ºC for 48 hours (Clifton et al. 2001). There was a suggestion that hypothermia is detrimental to subjects >45 years of age, but possibly beneficial for patients who were ≤45 years of age and who were hypothermic on admission. There was also significant variability amongst centres, particularly smaller centres.

Based on the subset analysis from NABIS:H, NABIS:H II was designed to enrol subjects who were 16-45 years old at select, experienced centres (Clifton et al. 2011). The intent was to induce hypothermia as early as possible after injury. This study did not demonstrate benefit of therapeutic hypothermia. Subset analysis of this study suggested that subjects with surgically-removed haematomas may have reaped greater benefit from hypothermia than those with diffuse brain injury.

Future studies may include stratification of patients by type of injury (focal vs diffuse). Previous studies have controlled temperature by protocol and found that intracranial pressure sometimes increased during rewarming. Titration of temperature based upon intracranial pressure during rewarming may be appropriate. Regardless of whether future studies demonstrate benefit of the induction of hypothermia, it is clear that

hyperthermia should be avoided as any fever can worsen neurologic outcomes. Controlled normothermia has become standard.

Spinal Cord Injury

Benefit of systemic, therapeutic hypothermia has been demonstrated in laboratory models of spinal cord injury (Inamasu et al. 2003). Clinically, hypothermia has been used for spinal cord protection during aortic surgery (Okita 2011). For traumatic, spinal cord injury, a randomised, clinical trial of therapeutic hypothermia is in progress (University of Miami).

Future Directions

A recent workshop sponsored by the U.S. National Institutes of Health and U.S. Army recommended additional studies to better understand the mechanisms of benefit of hypothermia, clinical impact of exposure hypothermia,

and interactions between hypothermia and potentially- beneficial drug therapies (Alam et al. 2012). Clinical trials are needed to explore the trauma settings for which hypothermia may have benefit, including haemorrhagic shock, cardiac arrest from trauma, traumatic brain injury, and spinal cord injury.

Published on : Wed, 25 Dec 2013