Adjuncts to Resuscitation

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Abstract

Damage control resuscitation has been increasingly adopted and practiced over the last decade. The concepts used are not new to this era of medicine but are novel in combination. This chapter will focus on adjuncts to damage control resuscitation (DCR) including massive transfusion protocols, the "other" tenets of damage control resuscitation, hypertonic saline, tranexamic acid, pharmacologic resuscitation, Factor VIIa, and prothrombin complex, and viscoelastic testing.

Damage control resuscitation (DCR) is a treatment strategy targeting the conditions that potentiate hemorrhage in the traumatically injured patient [1]. The term originates from the US Navy in reference to the techniques used to salvage a damaged ship during conflict [2]. In the management of the hemorrhaging patient, DCR refers to an approach to resuscitation initially adopted to improve outcomes of patients undergoing an abbreviated laparotomy or other procedure due to grossly disturbed physiology. However, its early implementation and even adoption in the prehospital setting have resulted in many of these patients now undergoing definitive procedures as the initial operation. The three basic tenets of DCR include permissive hypotension, blood product resuscitation approximating whole blood, and minimizing use of crystalloid prior to surgical control of bleeding [3]. Ideally, this process begins in the prehospital setting and continues through the emergency room (ER) and operating room, and into the ICU, as needed.

Looking at the incorporation of the other two principles (permissive hypotension and minimizing crystalloids) into a mature trauma center already incorporating a transfusion strategy approaching whole blood, investigators found an improvement in survival among emergent laparotomy patients [4]. Cotton and colleagues evaluated 390 patients who underwent damage control laparotomy and were managed with a red blood cell:plasma:platelet ratio of 1:1:1. The investigators found that after adoption of permissive hypotension and minimal crystalloids in the ED and operating room, blood transfusions were reduced, patients arrived to the ICU with less coagulopathy and acidosis, and survival was increased 2.5-fold. Duke et al. investigated the combination of a restrictive fluid resuscitation strategy and DCR. They reported a significant reduction in preoperative and intraoperative crystalloid administration with improvements

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in hospital and ICU length of stay, a reduction in operative room mortality, and a resultant decrease in overall mortality [5].

20.1 Permissive Hypotension

The concept of permissive hypotension has been debated for years. Maintaining the patient's blood pressure high enough for adequate organ perfusion yet low enough as to avoid exsanguination is the goal. In 1918, Walter Cannon and John Fraser warned of the blood loss that could occur by elevating a patient's blood pressure before a surgeon was available [6]. The endpoint for resuscitation prior to the availability of a surgeon in their study was between 70 and 80 mmHg systolic blood pressure. In his document entitled "Surgery in World War II, General Surgery", Dr. Beecher stated that "*When the patient must wait for a considerable period, elevation of his systolic blood pressure to ~85 mmHg is all that is necessary*" and that "*…one should consider himself lucky if a systolic pressure of 80 mmHg to 85 mmHg can be achieved and then surgery undertaken*" [7]. However, human studies validated the data produced by animal studies have been few [8, 9].

In 2002, Dutton and colleagues conducted a randomized trial of hypotensive resuscitation [9]. A total of 110 patients were randomized on arrival to a resuscitation targeting a systolic blood pressure of 70 mmHg or a systolic of 100 mmHg. Each resuscitation strategy was continued until definitive hemostasis was achieved. While no survival difference was noted, the authors found that aiming for SBP of 70 mmHg (vs. >100 mmHg) was safe in patients arriving with evidence of hemorrhage. Carrick et al. recently evaluated a similar strategy in trauma patients undergoing a thoracotomy or laparotomy [10]. Aiming for mean arterial pressure of 50 or 65 mmHg, the investigators continued this goal throughout the operating room course. The authors found that while blood loss and transfusions were less in the hypotensive group (50 mmHg goal), this did not translate into an improvement in 30-day mortality. Both studies, however, were quite small and their results may reflect a type-II error. As well, the benefits of reduced hemorrhage outweigh the possible detrimental effects of organ ischemia and reperfusion injury [11].

20.2 Minimizing Crystalloids

Historically, large quantities of crystalloid and blood were advocated to replace the intravascular and extravascular fluid loss from hemorrhage. This strategy arose from studies in the 1950s and 1960s and was, until recently, endorsed by the American College of Surgeons Advanced Trauma Life Support (ATLS) course with the recommendation of 1–2 L of crystalloid during the initial management of trauma patients [12–14]. However, multiple studies have shown the detriments of aggressive crystalloid resuscitation including cardiac dysfunction, ARDS, multi-organ failure, and increases in mortality [15–21]. Moreover, the infusion of room temperature, high chloride containing fluid worsens hypothermia, acidosis, and coagulopathy [22]. Resuscitation to a normal blood pressure increases hemorrhage through the dilution of coagulation factors, displacement of tenuous clots, and decreases in blood viscosity leading to increased mortality [23–28].

Evaluating the impact of minimizing crystalloids in the clinical arena, Bickell and colleagues built on this extensive preclinical data by conducting a randomized trial of standard ATLS resuscitation (crystalloids) versus no fluid [27]. Patients presenting with hypotension (systolic ≤ 90 mmHg) and who had sustained penetrating torso injuries were randomized to one arm or the other beginning in the prehospital setting and the randomization resuscitation strategies were continued until the patient entered the operating room. Patients who received no fluid (delayed resuscitation) had lower mortality compared to those who received immediate fluid resuscitation. Two decades later, the Resuscitation Outcomes Consortium further investigated these two damage control resuscitation principles [29]. The investigators randomized study patients beginning in the prehospital setting to a systolic pressure of 70 mmHg and small boluses (250 mL) to maintain blood pressure goal, while the control group was randomized to

110 mmHg, received two liters initially, and additional fluid to maintain blood pressure target. Each protocol continued until hemorrhage control or 2 h after hospital arrival. The 24-h mortality for blunt trauma was significantly lower in the study arm compared to that observed in the control group (3% vs. 18%).

Assessment of Blood Consumption Score
ED systolic BP ED systolic blood pressure ≤ 90 mmHg
ED heart rate ≥ 120 beats per minutes
Penetrating Mechanism
Positive fluid on abdominal FAST

Fig. 20.1 Assessment of blood consumption score

20.3 Massive Transfusion Protocolization

The 1970s brought about the first discussions of massive transfusions (MT) and the associated 90% mortality rate [30]. However, the development of standardized delivery processes and protocolization of these MT processes would take another 30 years to arrive. With the implementation and maturation of these MT protocols, times to delivery of initial blood products, overall product utilization, and mortality were all significantly reduced [31, 32]. To put this in perspective, early improvements in hemorrhagic shock resuscitation (2000–2005) had reported mortalities for patients receiving a MT were 55–65% [33]. However, with increased adoption of MT protocols, mortality soon dropped to 45–50% by 2009. With further maturation and adoption of DCR tenets, MT mortalities continued to decrease to the current rates of 22–26% [34].

The layers of delay for blood product administration include the placement of the individual product orders, communication among providers, decisions regarding the products to transfuse, transportation of blood samples to the lab, and receipt and review of the lab values [35]. MT protocolization allows members of the trauma team to focus on managing the patient and their injuries and be less worried about choosing, obtaining, and transfusion of blood products. That said, establishing a massive transfusion protocol is not an easy task (Figs. 20.1, 20.2, 20.3 and 20.4). This is a multidisciplinary process involving the Emergency Medicine Physicians, Trauma Surgeons, Anesthesiologists, Hematologists, and Blood Bank. In 2008, Cotton et al. first demonstrated an improvement in mortality with the simple implementation of the MT process at their hospital [32]. In 2009, Riskin and colleagues also noted an improvement in mortality, which they attributed to improved communication with the blood bank and time to blood product availability [36]. In order for MT protocol to be effective, a center must have thawed or liquid plasma available for immediate delivery and transfusion [37–39]. Determining the content of the MTP cooler is highly debated in the literature to this day. In a recent randomized controlled trial, resuscitation of red blood cells:plasma:platelets in a ratio of 1:1:1 demonstrated a reduction in bleeding-related mortality [34]. However, overall mortality was not improved. No matter the take on the current literature, delivery of a standardized MT protocol and compliance with that protocol has been shown to improve outcomes in these patients [40, 41].

Once in place, knowing which patients will benefit from activation of the MT protocol can be difficult. Multiple scoring systems have been developed to identify patients that may benefit from a MT protocol [33]. While the predictive value of each of these scores is good, many of these include laboratory values that are not readily available upon the patient's arrival to the hospital making these scoring systems less useful. To address this, the Assessment of Blood Consumption (ABC) score was developed in 2009. It utilizes data readily available upon a patient's arrival to the hospital. The four components of the score are: ED systolic blood pressure ≤90 mmHg, ED heart rate ≥120 beats per minutes, penetrating mechanism, positive fluid on abdominal ultrasound evaluation. Each criterion consists of one point. Scores ≥2 indicate activation of the MT protocol (Fig. 20.1). While the ABC score overestimates the need for MT protocol with a positive predictive value of 50–55%, products can be returned and restocked. More importantly, the negative predic-

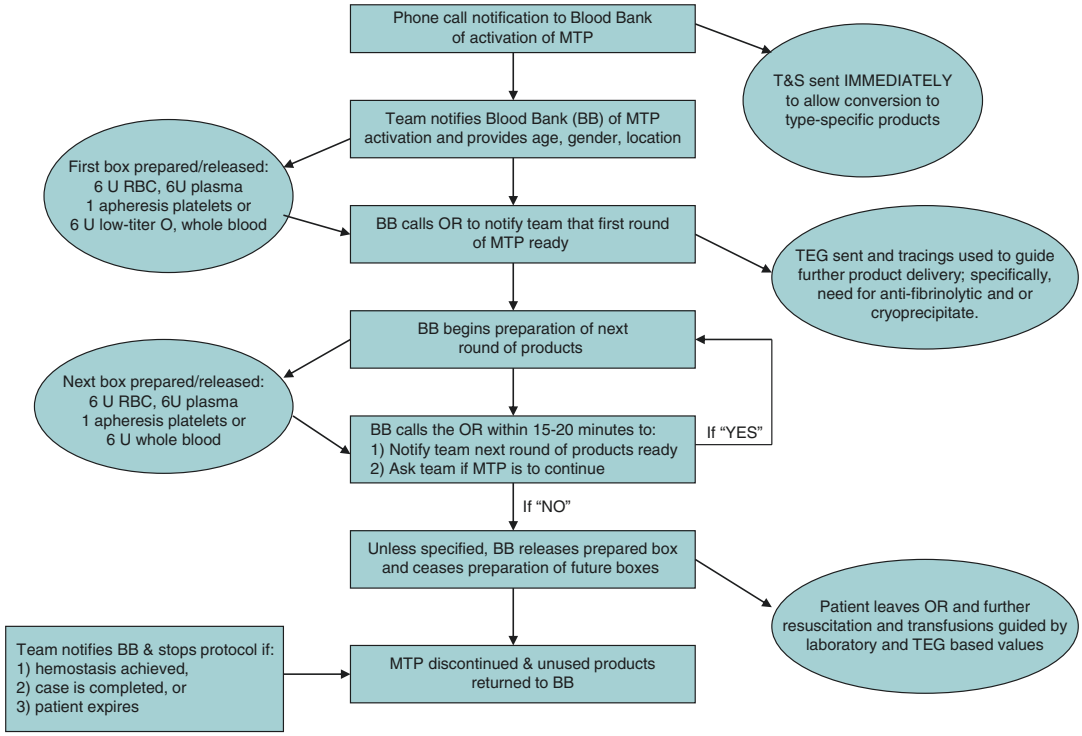

Fig. 20.2 Massive transfusion protocol at Memorial Hermann Hospital-Texas Trauma Institute

tive value for ABC is 95–96%; thereby minimizing those missed [39, 42, 43].

The ABC score is but one of many tools available to practitioners managing severely injured patients and should not replace a physician's discretion. Other clues to encourage activation of the MT protocol include persistent hemodynamic instability, active hemorrhage requiring surgical intervention, including interventional radiologic procedures, and the transfusion of non-crossmatched blood in the resuscitation bay [39]. A delay in identifying patients that require massive transfusion and delay in the initial cooler arrival, prolong the time to hemostasis and increase mortality [44, 45].

Once activated, the blood bank should immediately release MT coolers for transfusion approximately every 10–15 min. One simple rule: remain one cooler ahead of the current transfusion. Once the hemorrhage has been controlled and the patient is no longer hemodynamically unstable, the MT protocol can be discontinued. Laboratory indicators can be helpful in these situations and include hemoglobin levels, traditional coagulation tests, viscoelastic testing, platelet counts, and fibrinogen levels. The decision to terminate the MTP should be determined by the anesthesia and surgery teams jointly [39]. Compliance with the protocol is also essential for providing optimal care. Knowing when to activate and when to terminate the protocol can be guided by scoring tools and laboratory values. These values should assist, not replace, the judgment of the providers. The EAST guideline for damage control resuscitation recommends the development and implementation of a massive transfusion/DCR protocol in a multidisciplinary fashion with current literature and target blood product ratios. Furthermore, the same group endorses a high ratio MT/DCR strategy, if not whole blood [37].

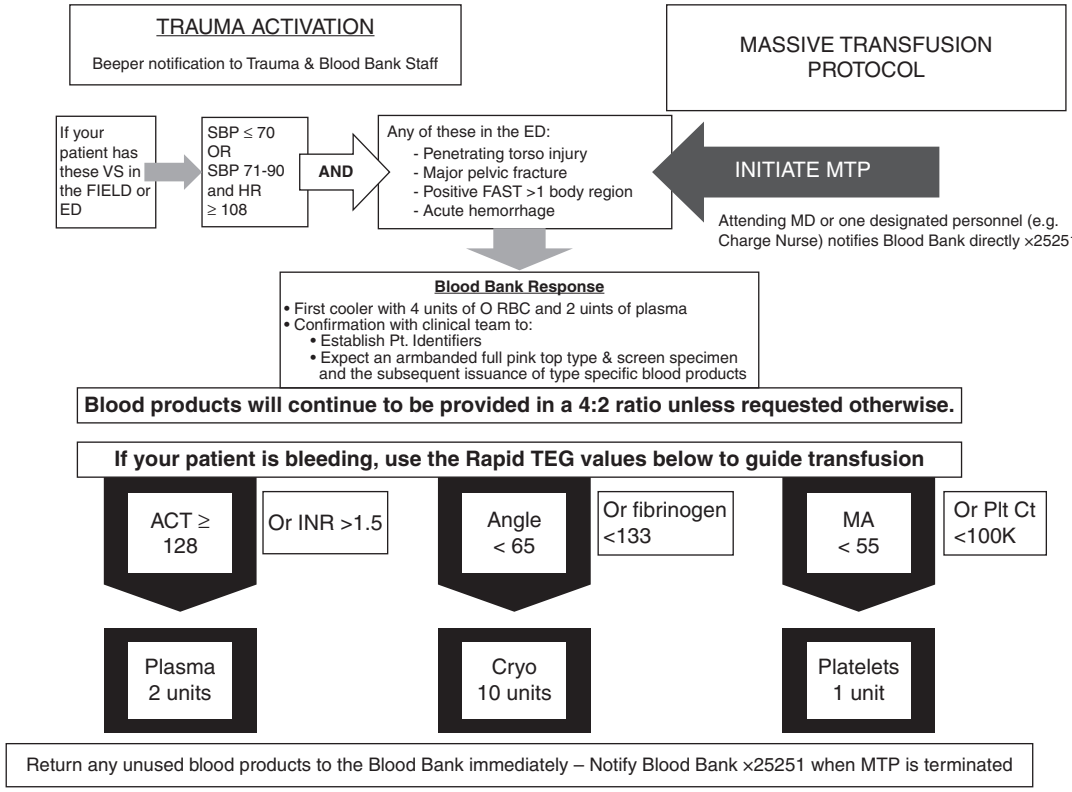

Fig. 20.3 r-TEG-based massive transfusion protocol at Denver HealthMedical Center

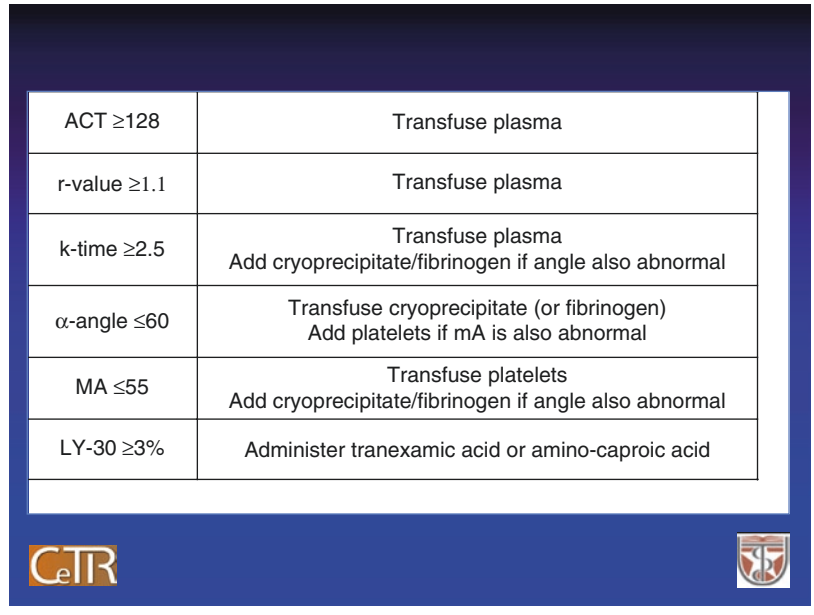

Fig. 20.4 r-TEG cut point values at Memorial Hermann Hospital-TexasTrauma Institute

20.4 Tranexamic Acid

The anti-fibrinolytic agent tranexamic acid (TXA) works by inhibiting the conversion of plasminogen to plasmin. In retrospective studies, administration of TXA to hemorrhaging patients has been associated with decreased mortality in both the civilian and military populations [46, 47]. It has also been shown to be a cost-effective adjunct for health care systems in poor and wealthy nations [48]. The identified window of benefit for the administration of TXA is within 3 h of injury [49]. However, TXA has failed to gain widespread acceptance and incorporation in the USA for multiple reasons. First, the large, multicenter, randomized trial of TXA in injured patients (CRASH-2) has several major methodological flaws. Also, whether TXA has any impact on trauma outcomes in a region already practicing DCR or a hospital with a MTP in place is unknown. The majority of patients enrolled in CRASH-2 were in low-income and middle-income countries where blood products, mature trauma centers, and experienced trauma teams are not readily available. Finally, how sick or injured (or uninjured) patients were in CRASH-2 is also a concern; less than half of patients (in either TXA or placebo groups) underwent an operation and only half received even one unit of blood.

In 2013, Napolitano et al. recommended TXA be used as part of a MTP in the following situations: (1) hyperfibrinolysis demonstrated on viscoelastic testing or (2) in patients with severe hemorrhagic shock (SBP $\leq$75 mmHg and a base deficit >5). Furthermore, given the increase in mortality seen with administration after 3 h, TXA should not be given when the time from injury is known or suspected to be greater than 3 h [50]. The current EAST guideline conditionally recommends TXA use as a hemostatic adjunct in the severely injured patient in the hospital setting only [37].

20.5 Fibrinogen Replacement

The case for the addition of fibrinogen, through either cryoprecipitate or fibrinogen concentrate, remains controversial. While in theory an argument can be easily made for its use in the bleeding patient, data in trauma and emergent cases is extremely lacking. The majority of data supporting its use is in the cardiac setting, and especially in those scenarios where intravascular support includes hydroxyethyl starches [51]. Hydroxyethyl starches reduce maximal clot firmness through a reduction in fibrinogen activity (as well as that of factors II, X, and XIII) [52]. One randomized trial of patients undergoing major aortic replacement surgery found a reduction in both red blood cell and plasma transfusions in patients receiving fibrinogen concentrate (compared to placebo) [53]. In the setting of trauma, Schochl et al. evaluated 131 patients who received fibrinogen concentrate guided by viscoelastic tests in the setting of bleeding [54]. The authors noted a significantly improved mortality compared to that predicted by the Trauma Related Injury Severity Score (TRISS) in patients who received fibrinogen concentrate during their initial resuscitation. As well, German investigators found that exsanguinating patients who received fibrinogen concentrate as part of their resuscitation had improved 6-h mortality (corresponding to the time of bleeding-related deaths [55]). The MATTERs II study, which was a retrospective study of UK and US military experience with combat injuries, evaluated the role of cryoprecipitate and tranexamic acid [56]. Investigators found that when patients received both cryoprecipitate and tranexamic acid as part of their care, mortality was half that of those who received neither (11.6 versus 23.6%). However, the PROMMTT investigators evaluated the impact of cryoprecipitate on bleeding patients from ten US Level-1 trauma centers and noted that its use varied greatly in their timing and use of cryoprecipitate in severely injured trauma

patients [57]. However, the authors could not identify any association of cryoprecipitate use with in-hospital mortality. In addition, some have argued that routine replacement even in exsanguinating patients is unwarranted [58]. Opponents note that with early and more aggressive use of plasma, hypofibrinogenemia and/or fibrinogen dysfunction is uncommon. Given this, most would agree that randomized controlled studies in trauma are needed to determine if fibrinogen replacement is necessary. To that end, a randomized trial of fibrinogen replacement beginning in the prehospital setting, CRYOSTAT-2, will begin enrollment in 2017.

20.6 Prothrombin Complex Concentrate

Prothrombin complex concentrate (PCC) is a concentrated vitamin K-dependent coagulation factor product. It was originally approved for the treatment of hemophilia B and has been expanded to the reversal of vitamin K antagonist (VKA) effects. PCCs offer potential advantages over plasma including faster INR normalization in patients, delivery of smaller infusion volume, rapid administration, and no requirement for ABO blood-type matching.

All derived from pooled plasma and carry the possible risk of virus transmission. The 4-factor concentrates contain factors II, VII, IX, and X, while the 3-factor concentrates contain II, IX, and X. Sarode and colleagues conducted a multicenter, randomized trial in non-trauma, noncritical patients who were on warfarin and had need for urgent INR reversal [59]. The authors demonstrated that PCCs more rapidly reversed INR compared to plasma reversal, and did so with a similar adverse event profile. Studies in trauma are small and few [60]. However, some of these have noted effectiveness of PCC in the rapid reversal of VKA-related coagulopathy in trauma patients. Quick et al. demonstrated the safety and efficacy of PCC in the reversal of VKA-related coagulopathy in geriatric trauma patients [61]. Huynh et al. noted a more rapid correction of INR in patients on warfarin who sustained traumatic brain injury, with no differences in outcome. The utility of PCC incorporation into MT protocols or as a replacement for plasma in early resuscitation remains to be answered. Plasma provides volume expansion, acid-base buffering capacity, and high oncotic properties, all of which are beneficial in the patient with hemorrhagic shock, and none of which are present with PCCs [58]. In addition, plasma is effective in maintaining vascular endothelium integrity and clot stability, which has not yet been established for PCCs [62].

20.7 Recombinant Factor VIIa (rFVIIa)

Recombinant factor VIIa (rFVIIa) is currently approved for the treatment of hemophilia and has previously been advocated for the use in hemorrhaging trauma patients. It has been adopted and incorporated into many massive transfusion algorithms [63]. The rFVIIa is thought to activate the common coagulation pathway at pharmacologic doses [64]. Several retrospective studies show possible benefit in the use of rFVIIa as an adjunct to DCR by decreasing the overall need for blood transfusions, improvement in traditional coagulation tests, and hastening the resolution of bleeding [65–67]. However, randomized trials were less encouraging. Bouffard et al. published a randomized, placebo-controlled trial showing that patients suffering from blunt traumatic injury received less blood products with rFVIIa, but no benefit was seen in penetrating trauma [68]. Raobaikady et al. reported their randomized trial on the use of rFVIIa during pelvic reconstruction and noted no difference in transfusion requirements [69]. In

2010, the CONTROL trial evaluated the safety and efficacy of rFVIIa in a multinational randomized trial. There was no difference in survival between patients receiving rFVIIa and placebo, regardless of the mechanism of trauma. Similar to previous studies, rFVIIa decreased red blood cells and plasma transfusions and a trend toward less multiorgan failure was noted [70].

There was much early enthusiasm for the use of rFVIIa in the management of the bleeding patient. However, the popularity of DCR, with less crystalloid volume and earlier plasma and platelet transfusions, increased during the study periods for rVIIa. The current EAST guideline does not recommend for or against the use of rFVIIa as it does not appear to improve all-cause mortality and the only benefit is a possible reduction in the need for massive transfusion. They recommend further study to identify the optimal dose and timing for rFVIIa delivery [37].

20.8 Vasopressin

Arginine vasopressin (AVP) is an endogenous neurohypophyseal hormone released in response to changes in plasma osmolality and blood pressure [71]. Hypotension can stimulate the release of vasopressin as much as 40 times physiologic concentrations. Also, AVP clearance is prolonged leading to higher concentrations for a longer duration [72]. Its release is suppressed by elevations of norepinephrine and nitric oxide, which can be seen in hemorrhagic shock. Primarily, AVP works on the extracerebral arteriole V1 receptors leading to vasoconstriction. This causes an increase in systemic vascular resistance and a redistribution of blood flow from capacitance vessels in the periphery toward heart, brain, and kidneys [73]. However, this vasoconstriction is not as great in the coronary and renal system. AVP potentially has a vasodilatory effect on cerebral and renal vessels leading to improved blood flow [74].

The compensatory increase in endogenous vasopressin levels has been described in septic and hemorrhagic shock. Patients suffering from septic or hemorrhagic shock with a depressed endogenous AVP response show a significant increase in blood pressure with low-dose administration of AVP, while patients with a normal compensatory response did not show the same response to low-dose AVP administration [75, 76]. Animal models of liver injury associated hemorrhagic shock have shown decreased blood loss, increased mean arterial pressure, and significantly higher hemoglobin levels with vasopressin administration compared to standard crystalloid resuscitation [74]. AVP caused a shift in blood flow from the intra-abdominal injury leading to decreased blood loss. A temporary shunting of blood flow from the mesenteric vessels and profound peripheral vasoconstriction lead to restored perfusion of the liver and kidneys [74, 77]. Similar studies showed an increase in cardiac and cerebral blood flow following vasopressin administration secondary to cutaneous, muscular, adipose, gut vasoconstriction. The cardiovascular collapse and blood loss seen with crystalloid infusion was not demonstrated following AVP injection [78]. A randomized, placebo-controlled study (AVERT Shock) is currently underway to investigate the potential benefit of vasopressin administration during the early resuscitation of bleeding trauma patients [79].

20.9 Valproic Acid

Valproic acid (VPA) is a GABA-ergic medication used in the treatment of epilepsy, bipolar disorder, migraines, and neuropathic pain. There are multiple mechanisms of action that contribute to the biologic activity of VPA including the alteration of gene expression, the downregulation of enzymatic pathways, the enhancement of neurotransmission, and the stabilization of neuronal membranes [80–83]. Histone deacetylase has been implicated in the modulation of the lifespan of certain organisms through its effect on gene expression [84]. Hemorrhage and the resuscitation of hemorrhage have been shown to be associated with an imbalance in histone deacetylase (HDAC) and histone acetyltransferase (HAT) activity. The presence of shock induces changes in histone deacetylation which can be reversed with the infusion of VPA, a HDAC inhibitor. Animal models have shown that the cytoprotec-

tive and restorative effects occur with pretreatment and post-injury infusion of VPA [85–87]. This leads to improvement in early survival from near lethal hemorrhage. The survival advantage is likely due to better tolerance to the shock state by cells [88]. Further research needs to be performed in this area to investigate the utility of VPA in human trauma resuscitation.

20.10 Hypertonic Saline

The infusion of hypertonic saline has been described at multiple points during the management of the injured patient; from the point of injury, to specific injury management, to damage control resuscitation. Hypertonic saline infusion increases serum osmolality causing a shift of fluid volume from the intracellular to the extracellular space. This volume shift effectively increases preload, cardiac output, and mean arterial pressure [89]. Mazzoni et al. described an improvement in capillary endothelial swelling leading to an improvement in microcirculation with the infusion of hypertonic saline [90].

As described above, volume overload is detrimental to patients requiring management in damage control situations. It leads to the development of acute lung injury and acute respiratory distress syndrome, as well as to multisystem organ failure secondary to the cascade of inflammatory and immune responses associated with volume overload [91]. Hypertonic saline infusion allows for the rapid restoration of preload with less volume. Furthermore, the edema associated with resuscitation is attenuated leading to improved end organ perfusion [1]. Animal studies have shown that hypertonic saline infusion attenuates the proliferation of white blood cells, endothelial adhesion, and the expression of inflammatory markers in the lung and gut [92–94]. Rizoli and colleagues corroborated these findings by demonstrating a decreased neutrophil activation, decreased serum TNF-α levels, increased level of anti-inflammatory cytokines IL-1ra and IL-10, and attenuated norepinephrine surge associated with shock. This was demonstrated up to 24 h following injury [95]. Other animal studies have shown that hypertonic saline not only prevents, but reverses resuscitation-induced intestinal edema [96–98].

Duchesne et al. performed a retrospective comparison of low volume resuscitation with hypertonic saline and isotonic crystalloid infusion during the ICU phase of damage control resuscitation. They found a decrease in the volume infused, decreased ICU length of stay, lower prevalence of ARDS and multisystem organ failure, and a trend toward renal failure in the hypertonic saline group [91]. In 2013, Harvin and colleagues described a protocol of hypertonic saline (3% saline) infusion following damage control laparotomy with respect to primary fascial closure. They found that the isotonic crystalloid group received significantly more fluid compared to the hypertonic saline group; however, transfusions of blood products were similar. There were also similar rates of renal failure between the group. The investigators found that 100% of patients in the hypertonic saline group achieved primary fascial closure by post-damage control day 7 and a decreased time to fascial closure compared to 76% in the isotonic crystalloid group [99].

20.11 Viscoelastic Testing

Approximately 25% of severely injured patients have an established coagulopathy upon arrival to the emergency department [100, 101]. Prompt recognition and treatment of this cohort of patients is crucial. Most centers monitor five convention coagulation tests: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), platelet count, and fibrinogen levels. These tests are representative of a portion of the coagulation system. Utilization of these tests is limited by slow result times, poor association with clinical outcomes, and incomplete characterization of the complete coagulation system. Viscoelastic tests characterize the lifespan of a clot from the time to initial fibrin cross-linking to breakdown by fibrinolysis in a single assay [102]. The viscoelastic assays available are thromboelastography (TEG) (Haemonetics Corp, Niles, IN) and thromboelastometry (ROTEM) (TEM International, GmbH, Munich,

Germany). The rapid TEG (r-TEG) assay has been shown to be readily available within minutes of being drawn, correlates well with conventional coagulation tests, and is predictive of early transfusion necessity [103]. In 2012, Holcomb et al. found that r-TEG data was clinically superior to the five conventional coagulation assays and identified patients with an increased risk of early PRBC, plasma and platelet transfusions, and fibrinolysis. The authors suggested that admission conventional coagulation tests could be replaced with r-TEG [104]. Further investigation into specific TEG values found that the parameter of clot strength (G) provided a consistent, independent prediction of massive transfusion and coagulation-related mortality early in the resuscitation [105]. Most recently, Gonzalez et al. compared MTP goal-directed by TEG versus conventional coagulation tests. They found that using a goal directed, TEG-guided MTP improved survival and used less plasma and platelet transfusions during the early phase of resuscitation compared with conventional coagulation test directed MTP [106].

Conclusions

Damage control resuscitation has become increasingly adopted and practiced over the last 10 years. While many of the concepts used are not new, their application to early trauma resuscitation and their combination unique "cocktails" is novel, and the resultant improved outcomes applauded. This chapter evaluated many of these adjuncts to DCR including massive transfusion protocols, the less known and investigated DCR tenets, viscoelastic testing, hypertonic saline, tranexamic acid, Factor VIIa, and prothrombin complex.

In conjunction with early use of blood products (in ratios resembling whole blood), permissive hypotension and limited crystalloid administration are associated with reduced bleeding, less transfusions, and improved survival. Protocolization of the massive transfusion process, independent of ratios and products, is associated with improved survival. Use of viscoelastic testing to guide the resuscitation or bleeding patients appears to improve survival and reduce overall transfusion rates.

While VIIa and PCC appear to be of little use in the acute resuscitation of hemorrhage, TXA appears to improve survival in patients with penetrating mechanism, who are in profound shock, and receive the drug early after injury. Both hypertonic saline and vasopressin hold promise in the pursuit to limit fluid resuscitation and bleeding volume in hemorrhagic shock patients. Finally, use of valproic acid may not reduce bleeding but may allow for better tolerance of prolonged hemorrhagic shock, allowing for the delivery to appropriate levels of care for severely injured patients.

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