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Evolving Trends in Trauma Resuscitation

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1. Abstract

Trauma remains the major cause of years of potential life lost for those less than 44 [1]. It impacts young and old alike with falls in the elderly being the most common cause of an injury admission in the current era [2]. Mortality related to an acute injury usually presents early in the hospital course. Uncontrolled hemorrhage and traumatic brain injury are the two most common causes of death during the initial 24-48 hours of hospitalization [3,4]. Fatal brain injuries are in large measure related to uncontrolled intracranial hypertension and herniation. Exsanguinating hemorrhage is related to the severity of the injury, the vascular structures violated and the ability of the surgeon to obtain control. There are a number of ancillary factors that may contribute to hemorrhage. Eliminating these factors may provide the injured patient an improved chance at survival. This article will review contemporary issues in trauma resuscitation and highlight current techniques that have been introduced to address non-compressible hemorrhage.

2. Materials and Methods

National Institute of Health's National Medicine library data base PubMed and Cochrane Reviews were queried for English language articles with key words: trauma resuscitation, coagulopathy, damage control resuscitation and hemostasis. 180 Pubmed articles were identified and 17 Cochran reviews noted. 120 total articles were selected for review and a comprehensive analysis in the following areas; factors contributing to hemorrhage, hemostatic resuscitation, damage control techniques, metabolic resuscitation, return to homeostasis and new horizons was performed.

3. Factors Contributing to Hemorrhage

The lethal triad of hypothermia, acidosis and coagulopathy has been recognized as a major cause of mortality in the setting of hemorrhage from acute injury. The presence of hypothermia increases the risk for hemorrhage with every degree drop of temperature below 36 degrees [5]. Correcting hypothermia will decrease bleeding risk as platelet function can be restored in the setting of normothermia [6]. Coagulation factors also exhibit improved function in a normothermic setting [7].

Coagulopathy contributes to bleeding risk. It is estimated that 25% of injured patients will exhibit evidence of coagulopathy on admission [8]. Most do not have hyperfibrinolysis but for those that do early intervention with a plasminogen inhibitor may slow bleeding and increase the chance for survival [9]. Observational data in a cohort of bluntly injured trauma victims has documented catecholamine induced trauma endotheliopathy that contributes to a bleeding diathesis [10,11]. This "endotheliopathy" involves compromise of the glycolcalyx layer and endothelial cell injury. The treatment for this is factor replacement, on-going resuscitation and elimination of the inciting event. Plasma administration in the pre-hospital phase may be protective but this has not been proven.

Continued shock with ensuing acidosis represents the final element of the lethal triad [acidosis, coagulopathy and hypothermia]. The clinician is faced with the task of detecting shock early and implementing therapy quickly. Shock remains a clinical diagnosis and in trauma is usually explained by blood loss. The ATLS protocol provides the emergency room physician and surgeon with a working template of blood loss sources. Blood on the floor, plus four more is the aphorism that reflects sources of hemorrhage including chest, abdomen, pelvis/retroperitoneum and major long bones [12]. The initial focused abdominal ultrasound for trauma evaluates the pericardium, right upper quadrant, left upper quad-

rant and pelvis for the presence of blood loss. The plain films of the chest and pelvis will highlight these areas as sites of blood loss and the clinician must respond accordingly. An open book pelvic fracture will be addressed with a pelvic binder, a hemothorax with a chest tube and blood product replacement and intraabdominal hemorrhage with a rapid trip to the operating room for exploration. It is important to note that pulse pressure [the difference between the systolic and diastolic pressures] has emerged as a useful tool in the tachycardic patient without hypotension. In a group of 173 trauma patients – a narrow pulse pressure correlated with the need for transfusion [13]. In a small study of human volunteers applying increasing amounts of lower body negative pressure caused a linear reduction in pulse pressure and stroke volume along with an increase in muscle sympathetic nerve activity [14]. A narrow pulse pressure may be a clue that on-going blood loss is an issue. Various lifesaving interventions including transfusion and airway maintenance should be addressed without delay.

The need for Life Saving Interventions can be predicted by the presence of hypotension and a GCS motor score of less than 6. In a small series when these two findings were present 95% of the patients required life-saving interventions [15,16]. Determining the need for massive transfusion at the outset of care is important. Appropriate resources can be mobilized and rapidly deployed for patients in need of this critical intervention. Various tools have been suggested to aid in recognition. The Assessment of Blood Consumption is a scoring system based on the presence of 4 parameters: hypotension [systolic less than 90 mm Hg], an elevated pulse [greater than 120], penetrating trauma and a positive FAST. Each parameter receives one point in the scoring system and a total score of 2 or above is associated with the need for massive transfusion. [17]. Critical Administration Threshold is another metric that has been used to predict the need for massive transfusion [18]. If more than 3 units of Packed Red Blood cells are needed within the first hour, implementing a massive transfusion protocol is usually required. Resuscitation Intensity [defined as the total amount of fluid, blood and component therapy given within the first 30 minutes of hospitalization has high specificity, high positive and high negative predictive value in determining the need for massive transfusion [18].

Shock index [pulse rate divided by blood pressure] provides a useful signal for patients injured in a rural setting with prolonged pre-hospital transport. In a recent study initial shock index was a predictor of the use of blood transfusion and the need for intensive care at the time of admission [19]. All of these metrics provide the clinician with information that may help to guide therapy during resuscitation.

4. Hemostatic Resuscitation

There are several studies examining the role of hemostatic resuscitation in the treatment of patients with massive hemorrhage. The Prospective Plasma, Platelet and Packed Cell ratios or PROPPR trial evaluated 680 seriously injured patients who received massive transfusion [20]. This randomized study compared a 1:1:1 ratio [plasma, platelet, red cells] to a 1:1:2 ratio. There was no difference in 24-hour mortality or 30-day mortality between the two groups. A post-hoc analysis revealed that patients who received the 1:1:1 resuscitation were less likely to die from exsanguination. Another study looking at more than 4,000 trauma patients who received massive transfusion within 24 hours documented that a fresh frozen plasma to packed red blood cell ratio of 1:1 was associated with the lowest mortality [21]. The odds of mortality independently increased to 1.23 for a 1:2 ratio, 2.11 for a 1:4 ratio and 4.11 for a 1:5 ratio. The ratios achieved were the same at 4 hours and at 24 hours. This finding effectively refutes the theory that survivor bias explains the difference between the ratio outcomes. These studies serve as a background for understanding the principles associated with Damage control resuscitation. First, one must avoid large crystalloid infusions [22]. In a cohort of 197 patients a controlled resuscitation strategy that limited crystalloid administration early was associated with an improved outcome [23]. Second, Blood replacement should be performed to simulate whole blood with a PRBC:FFP:Platelet ratio of 1:1:1. [23]. Third, permissive hypotension is reasonable if the patient is on the way to the operating room for definitive care [24]. Several studies document improved physiology [corrected base deficit and lactate] on admission to the ICU in those patients who were treated with a hemostatic resuscitation protocol during damage control laparotomy [25,26].

Some researchers have attempted to refine resuscitation further by utilizing goal-directed resuscitation with thromboelastography to limit platelet and fresh frozen plasma therapy [27,28]. We now have international data evaluating the use of Visco-hemostatic assays [TEG, ROTEM] in the management of patients with massive transfusion. The ITACTIC -Implementing Treatment Algorithm to Correct Trauma Induced Coagulopathy trial documented that a viscoelastic hemostatic assay was most helpful in patients with moderate traumatic brain injury [29]. Overall, there was no mortality difference in those assessed with VHA versus conventional coagulation tests but in the subset of traumatic brain injury mentioned there were improved outcomes [29]. This data must be placed within context. The resuscitation may begin with the 1:1:1 paradigm but this likely should change once hemostasis has been achieved and more data regarding, temperature, acidosis, clot strength and lysis is obtained. It is also important for the surgeon to visually assess clotting. Observing coagulopathic bleeding in the operating room should factor into decision making. Monitoring temperature, correction of acidosis and correlating the Visco-hemostatic assay with the clinical status in real time is the ideal.

As noted previously component therapy using the 1:1:1 ratio is designed to simulate the administration of whole blood. There is sol-

id data on the use of whole blood itself in resuscitation. The military experience with whole blood administration has been positive [30,31]. In the civilian setting there is a strong push to administer more whole blood early in the resuscitation period. A single center experience evaluated whole blood administration in 1,377 patients in shock receiving emergency release uncrossmatched blood. The whole blood patients had higher injury severity and higher baseline lactate levels at the time of arrival. When compared to component therapy group, the whole blood patients had a 60% reduction in transfusions. Similar survival was noted between the two groups [32]. National Trauma Quality Improvement Program [TQIP] data documents that whole blood administration in conjunction with standard component therapy is associated with lower mortality at 24 hours, lower hospital mortality, lower major complications and a shorter length of stay [33]. A singe center experience with whole blood combined with component therapy found a shorter duration of mechanical ventilation and a decreased incidence of ARDS when compared to component therapy alone [34]. Low titer group O whole blood appears to be safe for all blood types [35]. Preliminary pediatric data using a propensity matched analysis suggests that whole blood is safe and is associated with rapid shock reversal when administered to acutely injured children [36]. An additional study using TQIP data compared 135 children receiving whole blood and component therapy to component therapy alone. Total blood products transfused were decreased in the whole blood group with no difference in overall complications or length of stay [37]. These results emphasize the safety and efficacy of whole blood administration in adult and pediatric patients.

Fibrinogen remains a critical coagulation factor in the formation of a stable clot. Low fibrinogen levels may contribute to the coagulopathy of acute injury [38]. The decrease in fibrinogen may reflect on-going fibrinolysis, severe tissue injury and shock [39]. The early administration of cryoprecipitate has has been proposed as a possible solution to this problem. Cryopreciptate has a much higher concentration of fibrinogen when compared to fresh frozen plasma. It also contains factor XIII and plasminogen activator inhibitor 1. These factors help to stabilize the clot and limit fibrinolysis [40,41]. Timing of administration and dosing may be potential barriers to its use. The Cryostat 1 trial has demonstrated that cryoprecipitate can be administered within 90 minutes of hospital arrival and correlates with improved fibrinogen levels [42]. The FEISTY 1 trial [Fibrinogen implementation early in severe trauma study] was a prospective trial from 4 hospitals in Queensland Australia, comparing the administration of cryoprecipitate with fibrinogen concentrate. This trial confirmed the rapid administration of fibrinogen concentrate within one hour of admission [43]. It was not designed or powered to answer the critical question of improved outcome with correction of serum fibrinogen. The Cryostat 2 trial is designed to determine if early cryoprecipitate administration is associated with improved outcomes [44]. A substudy of the FEISTY trial evaluated in vitro clot strength and porosity from a small cohort of the trial participants. The fibrinogen concentrate used did not have any added factors [like Factor XIII]. The clots from the patients receiving cryoprecipitate were stronger and less porous when compared to those from patients receiving fibrinogen concentrate only. This data provides additional theoretical support for utilizing cryoprecipate[45].

The role of additional adjuncts like Prothrombin Complex Concentrate [PCC] in the setting of massive transfusion is unclear. A propensity scores matched study comparing PCC and FFP to FFP alone demonstrated that PCC may decrease fresh frozen plasma use [46]. A 3-year analysis of TQIP data has reviewed the role of PCC combined with whole blood in the acute transfusion setting. The addition of PCC decreased the amount of packed red blood cells and fresh frozen plasma transfused [47]. PCC has a critical role to play in patient with traumatic brain injury who also have prolonged coagulation parameters related to coumadin or other drugs. Correcting INR quickly and with limited volume infusion are the main advantages of PCC. Factor 7 has been used to correct INR in patients anti-coagulated with warfarin. Its' use was explored for blunt or penetrating trauma patients who required massive transfusion. A mortality benefit was never achieved in penetrating trauma and because of expense it is not frequently used today [48].

5. Damage Control Techniques

Controlling blood loss and minimizing contamination of the peritoneal cavity acutely is the surgeons' charge. Liver packing and planned re-exploration was part of the early work in this arena [49]. Rotondo et.al advocated a damage control approach for the most critically ill subset – those with severe vascular injury in association with hollow viscus or solid organ injury [50]. This seminal work has stood the test of time. The concept of shortening the operating time, limiting hypothermia and reversing coagulopathy quickly serves as a foundation for this approach. The introduction of the negative pressure dressing has provided a rapid way to leave the abdomen open while protecting the viscera and achieving drainage. [51,52]. The scheduled return to the operating room when physiology has improved and coagulopathy corrected [usually within 24 -48 hours] achieves definitive treatment of injuries and formal closure of the abdomen. Overall recovery is hastened when primary closure of the abdomen is achieved [53,54]. The risk of enterocutaneous fistula is reduced as is the long-term sequelae of a large ventral hernia [55,56]. Direct Peritoneal Resuscitation [DPR] is essentially peritoneal dialysis that is started in the post-operative period to achieve a negative fluid balance and facilitate closure of the abdomen [57]. Animal data documents improved visceral blood flow when direct peritoneal resuscitation is combined with plasma administration. Intestinal integrity was maintained in rats subjected to shock who then received DPR and FFP [58]. The theoretical basis for its' use is solid but it has not found widespread application yet given the technical requirements for implementing it. Resuscitative thoracotomy is a lifesaving pro-

cedure that usually is performed via a left anterolateral approach. Its goal is to decompress the pericardium, cross-clamp the aorta and preserve circulation to the core and brain in a patient who has arrested or is about to. Recent data suggests a survival of 6% with either the left anterolateral approach or the trans-sternal and right chest extension – referred to as a clam shell thoracotomy [59].

Resuscitative Balloon Occlusion of the Aorta [REBOA] is an emerging technique designed as an adjunct to facilitate hemostasis in hard to control bleeding areas of the torso [60]. Patients with non-compressible abdominal hemorrhage are potential candidates. The technique involves vascular access in the common femoral artery with placement of a 7 french introducer sheath and subsequent deployment of the balloon catheter to Zone I – intrathoracic aorta below the take-off of the left subclavian] or Zone 3 deployment above the abdominal aortic bifurcation [61]. Advances in technology – [more compliant balloons] have made this a practical technique in the trauma bay. It is utilized as bridge therapy providing precious time to get the patient to the operating room or the angiography suite for definitive hemostasis. Registry data suggests that it does not improve outcomes in patient who arrest prior to arrival to the hospital or those who arrest in the trauma bay [62]. Currently indications for use include hypotension in the setting of blunt abdominal trauma with pelvic or intraabdominal hemorrhage. Pre-hospital data provides clues as to who may benefit. Using data from a level 1 trauma center patients were deemed candidates for pre-hospital Reboa if they had abdominal or pelvic injuries and no severe head injury. Using logistic regression, initial GCS of greater than or equal to 9, an oxygen saturation of more than 90% and a systolic blood pressure of less than 90 mm Hg were statistically associated with Reboa candidacy [63]. Patients with significant hemorrhage from pelvic fractures may accrue benefit from early Reboa application. In an analysis of TQIP 2017 data. Reboa was compared to pre-peritoneal packing [PP]. Patients were equally divided into pre-peritoneal packing, reboa, and PP plus reboa groups. Mortality and blood requirements were lowest with Reboa alone [64]. A retrospective report of Reboa application in a small cohort of severely injured pelvic fracture patients [mean ISS-44] documented a reliable increase in systolic blood pressure with inflation of the device [65]. This may not translate uniformly into improved survival though.

As with any device, there are complications related to insertion [arterial dissection, thrombosis, misplacement, migration] and complications related to use – acute kidney injury, increased limb loss and death [66,67,68]. Partial occlusion, shorter interval application is being explored as solutions to some of the issues related to low flow and metabolic derangements [69]. Uncontrolled vascular injuries above the area of deployment are cited as contraindication to the use of this technology. Although, one trauma center is using a two-team approach with a team assigned to gain vascular control in the chest followed by deployment of the Reboa. Preliminary results suggest that there is benefit to this approach [70]. Additional contraindications to Reboa deployment include intracranial hemorrhage and severe cerebral edema. Reperfusion injury is best treated by a protocol that addresses the acidosis, hyperkalemia, hypocalcemia and hypoglycemia that may occur after the balloon has been deflated [71]. Civilian use of extremity tourniquets for bleeding control in the pre-hospital setting has achieved excellent results. Decreased mortality, blood use, limb loss and limb morbidity have been documented with this approach [72,73].

Junctional tourniquets applied in hard to control bleeding areas have been used in the military field setting. There is no large experience with civilian use to date though [74]. Expandable foam is another technique for vascular injuries at the groin. It is injected directly into the gunshot wound site and expands on contact with body fluids. It must be removed in its' entirety after completing the vascular repairs with radiographic confirmation [75].

Expandable foam is also being assessed for non-compressible truncal hemorrhage. It is injected into the peritoneal cavity and it hardens with exposure to warm blood. It can be removed at the time of formal exploration. Animal studies have documented bowel injury and this may ultimately limit this approach [74]. Time to definitive hemostasis has been proposed as a quality metric regarding trauma resuscitation. In the PROPPR cohort 468 of the 680 enrolled patients underwent emergency procedures. In 408 of these patients in whom hemostasis was achieved every 15-minute decrease in time to hemostasis was associated with a decreased 30 day mortality. Morbidity measures such as sepsis, ARDS and multi-organ failure were decreased as well [76]. Another study combining PAMPR [pre-hospital plasma]and STAMP [study of TXA in pre-hospital period] trial data revealed that every one-minute increase in time to early resuscitative intervention was associated with a 2% increase in the odds of 30-day mortality [77]. Both studies emphasize that obtaining hemostasis early in the hospital care [or during the pre-hospital phase] can save lives.

6. Metabolic Resuscitation

Once the patient has returned to the intensive care unit from definitive surgical intervention the circulatory physiology is assessed. Mild hyperdynamic parameters are expected with an increase in cardiac output, a slight decrease in systemic vascular resistance and a normal arterio-venous oxygen difference. Serum lactate should correct rapidly [78,79]. Delayed resolution of lactic acidosis is associated with increased morbidity and mortality. Failure of lactate to clear should raise the issue of intestinal ischemia, liver compromise or inadequate resuscitation. Vasopressors are off and maintenance fluids and nutritional support should be part of an on-going protocol of care. Correction of serum phosphate, magnesium, potassium and calcium should be considered part of metabolic resuscitation. Calcium is an important mineral essential for

adequate coagulation and should be checked as part of the massive resuscitation protocol but also in the aftermath of a successful resuscitation. The ionized calcium is the important variable as the total serum calcium may be reduced along with the serum albumin [80]. Replacement should be guided by the ionized calcium result. Calcium should be administered in those patients with high serum potassium as a first line agent to prevent asystole. Serum magnesium must be checked and replaced as needed as well. Phosphate may be reduced as part of the refeeding syndrome [81]. It must be replaced to ensure adequate diaphragm function [82]. Post-operative fluids must be carefully selected. The SMARTT study documented a decrease in bicarbonate and an increase in chloride with a trend toward more acute kidney injury in those patients treated with normal saline [83]. Although this was a single center experience covering multiple units, the association of increased chloride with Acute Kidney injury has been raised by others [84,85]. With this in mind, lactated ringers should be considered as a replacement fluid. The Cristal study evaluated fluid choices in hypotensive ICU patients. No differences between colloids and crystalloids were detected early but the 90-day mortality data favored colloids [86]. Nutritional support remains a key feature of metabolic resuscitation. Enteral feedings are best. Maintenance of mucosal integrity and a decrease in nosocomial infection risk are some of the benefits of enteral nutrition [87,88].

7. Return of Homeostasis

Despite balanced resuscitation, post-operative fluid overload remains a major issue with significant sequelae. A two- liter positive fluid balance at 48 hours has been associated with an increased risk of ARDS and acute lung injury [89]. A positive fluid balance has been correlated with poor outcomes for patients with established acute lung injury and or ARDS [90]. Achieving a negative fluid balance with the use of diuretics or other techniques like continuous renal replacement therappy [CRRT] may help to protect the lungs and result in a less complicated post-operative course [91]. CRRT has several advantages. It provides a way to achieve negative fluid balance in spite of the need to administer large amounts of fluids. It provides creatinine clearance and may assist with metabolic support [92]. Myoglobin clearance may be another advantage of CRRT in patients with severe rhabdomyolysis and acute kidney injury [93,94]. It may result in platelet sequestration and destruction though and this may limit its' application [95]. Third space fluid mobilization by the third to fifth post-operative day is a part of the body's attempt to achieve homeostasis. A carefully constructed protocol using diuretic therapy may achieve negative fluid balance quickly [96]. Aggresive diuretic therapy may produce hypernatremia, hypokalemia and even hypomagnesemia. These abnormalities must be anticipated and corrected or prevented. We can facilitate this by using de-resuscitation techniques judiciously.

8. Remote Damage Control

Bringing advanced resuscitation techniques to the patient in the pre-hospital phase may be life-saving and efforts to do so are underway. One study has noted a positive outcome of lyophilized plasma in the pre-hospital setting [97]. The PAMPR trial documented improved outcomes in patients given fresh frozen plasma in route to trauma centers in a randomized trial [98]. These were primarily bluntly injured patients with significant pre-hospital transport times. These results were not duplicated in a more urban setting and indeed with a different patient population one study noted the mortality was actually increased in those patients who received pre-hospital plasma [99]. The objective of remote damage control is to interrupt endothelial injury early thus preventing "blood failure" and the life-threatening sequelae. A recent randomized open label trial of the use of packed cells and lyophilized plasma compared to a normal saline group in the pre-hospital period in 4 United Kingdom trauma

facilities provide additional data [RePHILL study]. Using a composite primary outcome of mortality and lactate clearance, there was no statistically significant difference between the study group and the normal saline group [100]. This result probably means we still have much to learn about the ideal resuscitation in the pre-hospital period for patients who are bleeding.

9. Additional Hemostatic Adjuncts

Tranexamic acid has emerged as a useful adjunct in the pre-hospital phase. It is a lysine analogue that inhibits the formation of plasmin and thus functions as an anti-fibrinolytic agent. It has been used in the military setting and seems to improve outcomes even in the most seriously injured subset of patients [101]. Crash[Clinical Randomization of Anti-fibrinolytic in Significant Hemorrhage] 2 data suggested there was a survival benefit when it was administered quickly [102]. Crash 3 data suggests that it can improve outcome in patients with moderate head injury [103]. There may be another mechanism of action for TXA that impacts the integrity of the glycocalyx. In vitro data using umbilical vein endothelial cultures documents the destruction of the glycocalyx with the administration of hydrogen peroxide [oxidative stress] and epinephrine [catecholamine stress]. Early TXA administration proved effective at minimizing the shedding of glycocalyx [104]. This data provides another rational for the administration of TXA in the pre-hospital setting and possibly provides a way to prevent the evolution of further endothelial injury in the setting of shock.

10. New Horizons

There has been a longstanding quest to develop chemical adjuncts that might provide the patient in shock with an extra advantage at the cellular level. Intense research regarding genomic, proteomic and metabolomic changes associated with injury have occurred over the last decade. Predicting recovery has been part of the promise of these approaches. Thus far there are clear profiles of bluntly injured trauma patients that can be defined by gene expression studies. These patients are categorized regarding time to recovery with certain genes profiles predicting early recovery [105].

Similar studies have been performed with burn injured patients [106]. Metabolomic studies using mass spectroscopy on venous blood from bluntly injured patients within 24 hours can provide essential clues as to the development of chronic critical illness [107]. Differences in aromatic amino acid metabolism along with metabolites associated with oxidative stress were evident. 2 metabolites [phenylacetyl glutamine and trimethylamine n-oxide were useful for differentiating patients who died or developed chronic critical illness at all time points. Additional research using both proteomics, metabolic and biomarkers are illuminating possible mechanisms to explain the different trajectories of critically ill trauma patients. Those that recover and spend a short time in the ICU versus those that do not survive or have a prolonged ICU course. Cardiac damage biomarkers [like troponin] showed the greatest elevation combined with a pro-inflammatory profile and markers of endotheliopathy in those patients with a prolonged recovery [108]. This raises the potential role of beta-blockade early in the course of trauma care. Seminal work in burn injury has documented the blunting of hypercatabolism with beta-blockade [109,110]. There is powerful data regarding the protective role of beta-blockade in severe traumatic brain injury [111,112,113]. This may reflect the effect of propranolol in modulating the catecholamine response in acute injury. Animal data from a hemorrhagic shock-lung contusion-chronic stress model reveals that inflammatory cytokines [TNF, IL-6, C-reactive protein] are activated and that propranolol can reduce these markers through microRNA fragments that downregulate the inflammatory response [114].

Valproic acid [VPA] may provide a degree of cellular protection. It acts as a histone deacetylase inhibitor [HDAI]. Hemorrhagic shock can suppress histone acetyltransferase leading to excessive histone deacetylation. VPA prolongs survival in highly lethal animal models of hemorrhagic shock. It deactivates inflammatory mitogen activated protein kinase [MAPK], stabilizes tight and junctions and attenuates systemic effects of reperfusion [115, 116,117]. Using a swine polytrauma/shock model, VPA generates a prosurvival genetic profile emphasizing cellular growth and proliferation. Downregulated genes were associated with cell cycle checkpoint regulation, apoptosis signaling and inflammatory pathways [118]. The prospect of all of this lies in whether we can modulate the recovery time with chemical adjuncts like valproic acid [histone deacytalase inhibitor], beta-blockade [propranolol], steroids, doxycycline[matrix metalloproteinase inhibitor] or some other substance that can support the patient on the cellular level in the pre-hospital phase or early in their hospital course [119]. Cellular protection may blunt the ravages of ischemia-reperfusion and uncontrolled inflammation that many of our trauma patients face. We are not at the point where any of this is ready for widespread implementation but the possibility of “precision medicine” for trauma resuscitation remains intriguing.

11. Summary

Resuscitation of the acutely injured continues to develop. We have pushed the point of intervention closer to the initial time of injury by administering packed cells, plasma, TXA and other adjuncts to blunt the blood and endothelial barrier exhaustion associated with severe blood loss. A constellation of new techniques to achieve rapid hemostasis in patients who are exsanguinating are being utilized. The optimal timing and application of these techniques is being refined. We must critically review the literature for those emerging options that are best and constantly re-evaluate our current care in search of better outcomes.

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