INTRODUCTION: HISTORY OF HEMORRHAGIC SHOCK RESUSCITATION

The term “shock” originates from “choc,” which was coined by French surgeon Henri François Le Dran in the eighteenth century to describe the destructive impact of gunshot.\(^1\) It subsequently evolved to signify the suddenly worsening condition that can ensue after major trauma. In modern medical literature, shock denotes a lack of end-organ perfusion, which can result from multiple etiologies, but hemorrhage is the cause of acute hypovolemic shock resulting from nonburn trauma.

The first recorded human blood transfusion occurred in 1819,\(^2\) but its use did not become common until almost 100 years later when the discovery of blood types\(^3\) and development of techniques to crossmatch blood\(^4\) allowed for widespread use. Crystalloid became the standard resuscitation fluid used for hemorrhagic shock in the nineteenth and early twentieth centuries\(^5,6\) because of its availability and safety. However, with the high volume of severely injured combatants encountered during...
World War I (WWI), Allied physicians soon realized crystalloid transfusions resulted in “unsatisfactory” results because of dilution. They preferred using limited whole-blood transfusions to maintain a low blood pressure and rewarming the patient. This became the standard of care for resuscitation for the last 8 months of the Great War. WWII physicians described similar practices of giving enough whole blood to achieve a systolic blood pressure of 85 mm Hg, along with appropriate skin color and warmth, while working to quickly stop bleeding. They also used transfusions of recently developed reconstituted dried plasma to maintain blood pressure while preparing whole blood.

By the time of the Vietnam War, there was a renewed interest in crystalloid administration based on subsequently refuted basic science and animal models of hemorrhage shock that showed improved survival from infusing Ringer lactate (LR) before whole-blood transfusion. As a result, trauma patients began receiving increasing quantities of crystalloid. Simultaneously, new blood fractionation techniques were being developed that allowed for whole blood to be separated into units of red blood cells (RBCs), plasma, and platelets. The ability to treat multiple patients with one unit of whole blood and the risk of hepatitis associated with plasma at that time prompted medical leaders and groups to advocate for specific component blood therapy for all transfusions despite no rigorous studies demonstrating the effects of such therapy in massively bleeding patients. Although some studies performed at that time suggested “noninferiority in elective surgical cases,” not a single study showed hemostatic potential in bleeding patients. Blood bankers demonstrated that they could administer component therapy safely, not necessarily that they should.

Trends away from whole-blood transfusions and toward large-volume crystalloid and RBC resuscitation continued throughout the last three decades of the twentieth century as a result of studies that said LR and more than six units of RBCs could be used without causing coagulopathy, and others saying it was not important to augment blood transfusions with plasma or platelets unless there was clinical or laboratory coagulopathy. Another study declaring that it was safe to administer 2 L of crystalloid while waiting for blood was widely propagated when it was adopted by the Advanced Trauma Life Support course. Often forgotten is that these studies were conducted in patients receiving whole blood rather than RBCs and LR, as had become the standard practice in some busy trauma centers as early as the mid-1970s. Concerns about human immunodeficiency virus transmission and goals of therapy targeting “supranormal” resuscitation led to continued propagation of transfusing large volumes of only crystalloid and RBCs during the 1980s and 1990s despite new tests making blood transfusions safe and large multicenter trails that showed no survival advantage to supranormal resuscitation.

When examined critically, large-volume transfusion strategies resulted in increased morbidity including decreased intestinal perfusion along with increased abdominal compartment syndrome, cardiopulmonary dysfunction, multiple organ dysfunction, and death. At the same time, coagulopathy was being identified in severely injured patients, independent of resuscitation, and was found to be associated with increased mortality. As a result, military surgeons returned to resuscitation techniques attempting to replicate the whole blood used in previous wars by including high ratios of plasma and platelets to RBCs. Results from data collected during conflicts in Afghanistan and Iraq showed that patients who received high ratios of plasma to RBCs had improved survival compared with those who received lower ratios. As a result, the military developed damage control resuscitation (DCR) to reduce blood loss and coagulopathy. DCR is focused on limiting crystalloids, delivering whole blood or
high ratios of plasma and platelets, and maintaining permissive hypotension (Fig. 1). Massive transfusion (MT) protocols (MTP) were developed to achieve these goals of DCR and, in some instances, have been shown to improve survival independent of ratios. Finally, experts have recommended avoiding hypothermia and rapidly controlling hemorrhage with surgery and appropriate hemostatic adjuncts.52

**DAMAGE CONTROL RESUSCITATION**

**Limit Crystalloid**

Of all the three tenets of DCR, some trauma surgeons argue that the reduction in crystalloids over the last decade has had the greatest impact of improving survival. Despite decades of liberal use treating trauma patients, it is now known that infusing large volumes of crystalloid as a replacement for lost blood worsens the “vicious cycle of coagulopathy” resulting from hypoxia, acidosis, and hypothermia that was originally described 35 years ago.32,53 Intravenous fluids are known to dilute clotting factors,54 cool patients,55 and create acidosis.56 They also cause edema57,58 and end-organ dysfunction59 by disrupting cellular mechanisms and causing inflammation. This results in several complications including cardiac,44 respiratory,53 gastrointestinal,60 and immune dysfunction; decreased wound healing45, increased anastomotic leak44,61; abdominal compartment syndrome43,62; open abdomens53,63; hyperfibrinolysis64; and mortality.44,53,65 Limiting crystalloid also results in fewer overall blood transfusions for those with life-threatening injuries.66–68

**Permissive Hypotension**

The origins of the second tenet reach back to WWI and WWII, where physicians described increased blood loss and rebleeding when normal blood pressure is achieved before hemorrhage control.9,11 The protective effect of hypotension was confirmed in animal models that showed decreased blood loss and improved mortality with limited resuscitation.24,69–72 A study in swine demonstrated that rebleeding occurs at an average systolic blood pressure of 94 mm Hg and a mean arterial pressure of 64 mm Hg.73 Randomized controlled trials confirmed the improvement in mortality from delaying resuscitation to a normal blood pressure until after operative control of hemorrhage.74

![Fig. 1. The three tenets of DCR, brought together by massive transfusion protocols, and supported by several adjuncts.](image_url)
bleeding\textsuperscript{74} in penetrating\textsuperscript{75} and blunt trauma patients.\textsuperscript{76} A study in the 1990s from Houston randomized to receive prehospital fluid resuscitation (crystalloids) versus none in penetrating torso patients presenting with hypotension (blood pressure $\leq 90$ mm Hg).\textsuperscript{74} Fluid resuscitation in the “no fluids” arm was withheld until the patient entered the operating room. The patients who received delayed resuscitation had improved survival compared with those who received immediate fluid resuscitation.

**Balanced (1:1:1) Resuscitation**

The third and final tenet of DCR is the one that has been the most studied and most noted. The initial call to arms for DCR strongly advocated for a ratio of blood products that approximated whole blood (1:1:1).\textsuperscript{52} Following publication of the initial military experience describing improved survival for those receiving higher ratios of plasma to RBCs,\textsuperscript{53} the findings were replicated in the military experience\textsuperscript{77} and multiple retrospective trials in civilians.\textsuperscript{49,78-81} of those receiving a ratio or platelets: plasma/RBC (1:1:1). These studies included patients injured by blunt\textsuperscript{82} and penetrating\textsuperscript{83} mechanisms. The improvement in outcomes from plasma transfusions is attributed to decreasing inflammation, edema, and vascular permeability by repairing tight junctions and the glycocalyx of the vascular endothelium,\textsuperscript{84,85} in addition to improving platelet function and clot formation. Plasma also decreases blood hypercoagulability by modulating thrombin generation.\textsuperscript{87} A limiting factor in fresh frozen plasma (FFP) administration has traditionally been the 45 minutes required to thaw it before transfusion. Prethawed\textsuperscript{88} or liquid plasma\textsuperscript{89} can be used to decrease this time\textsuperscript{90,91} and 69% of level I and II American College of Surgeons Trauma Quality Improvement Program trauma centers now have plasma immediately available for MTP activations.\textsuperscript{92} This has been shown to allow for earlier transfusions, balanced resuscitation, decreased overall blood product transfusions, and improved mortality.\textsuperscript{90,95} Similar to higher ratios of transfused plasma, multiple studies have demonstrated improved survival for patients receiving balanced ratios of platelets.\textsuperscript{94-99} Platelet inhibition and dysfunction is common after brain injury\textsuperscript{100} and minor trauma.\textsuperscript{101} It is associated with increased morbidity and mortality\textsuperscript{102} because platelets improve wound healing, vascular integrity, and immune response.\textsuperscript{98}

With the accumulation of trials demonstrating improved outcomes with balanced resuscitation, these practices quickly spread to civilian trauma practices throughout the United States, with MTP using a 1:1:1 ratio of plasma/platelets/RBCs blossoming from just a few institutions a decade ago\textsuperscript{103} to more than 85% of major trauma centers today.\textsuperscript{104} Retrospective reviews from trauma centers that implemented DCR showed an almost 50% reduction in crystalloid use at one center,\textsuperscript{105} whereas another showed significantly less use of crystalloid and all blood components.\textsuperscript{53} DRC is also associated with decreased morbidity from abdominal compartment syndrome,\textsuperscript{83,105} infection,\textsuperscript{105} and organ failure\textsuperscript{106} and reduced mortality\textsuperscript{53,105} from hemorrhage.\textsuperscript{107}

In 2009, a study examining the time to transfusion of different blood components demonstrated a limitation of retrospective studies. Because of the time required to thaw FFP, the time to first transfusion of FFP (93 minutes) was significantly greater than the time to first RBC transfusion (18 minutes), despite attempting to achieve balanced ratios. As a result, patients who died early received RBCs but were not able to receive the appropriate ratio of FFP and platelets to achieve a balanced transfusion. In contrast, those who survived were eventually able to achieve the goal ratios, thus creating a survival bias.\textsuperscript{108} The PROPPR trial was designed as a prospective, randomized, multicenter trial to overcome the selection bias of retrospective trials by evaluating the two most common resuscitation ratios\textsuperscript{99} as determined by the
PROMMTT study, which observed transfusion practices in 10 level 1 trauma centers. Although the PROPPR study showed no improvement in 24-hour survival for 1:1:1 versus 1:1:2 (plasma/platelet/RBC), it did show less death from exsanguination at 24 hours for higher ratios of plasma and platelets (9.2% in 1:1:1 group vs 14.6% in 1:1:2 group) and found no difference in complications for the group receiving higher ratios of plasma and platelets, alleviating concerns about their transfusion. The balanced plasma to RBC group also had decreased mortality at 3 hours, which is the median time to hemorrhagic death.

ADJUNCTS TO DAMAGE CONTROL RESUSCITATION

Whole Blood

Whole blood is the optimal resuscitation fluid for patients who are massively bleeding. After first being successfully used to treat hemorrhagic shock in WWI, military doctors have successfully transfused more than a million units of whole blood during conflicts over the past century and it was preferentially used in civilian trauma until the 1970s when it fell out of favor because of concerns about safety and waste. Recent military conflicts in Iraq and Afghanistan led to a resurgence of whole blood where more than 10,000 units were transfused to the most severely injured patients. Retrospective reviews of those who were transfused with warm fresh whole blood showed that it increased 24-hour and 30-day survival when compared with balanced component therapy. These findings are supported by an in vitro study that showed whole blood is more hemostatic and a pilot prospective randomized trial that showed it resulted in less transfusions of RBC, plasma, and platelets when patients with nonsurvivable head injuries were excluded. The reason for the superiority is that a 500-mL unit of fresh whole blood has a hematocrit of 38% to 50%, a total of 150,000 to 400,000 platelets per microliter with full activity, and 100% activity of clotting factors. By comparison, transfusing one unit of plasma, platelets, and RBCs results in 660 mL of fluid with a hematocrit of 29%, a total of 88,000 platelets per microliter, 65% coagulation factor activity with reduced flow characteristics, and increased additives including anticoagulants (Table 1).

Massive Transfusion Protocols

Based on experiences in WWII, Beecher wrote, “about 2.5% (sic) of those wounded would fall into the group that is in bad enough condition to require special resuscitative care.” That proportion of civilian trauma admissions currently requires more than 10 units of blood within 24 hours of admission, but two to three times that percentage of injured modern military combatants require an MT. The mortality for patients

<table>
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<td>Comparison of whole blood unit versus component therapy (reconstituted whole blood)</td>
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<tr>
<td>Volume, mL</td>
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<tr>
<td>Hematocrit,%</td>
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<td>Platelet count</td>
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<tr>
<td>Coagulation factors, %</td>
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<td>Fibrinogen, mg</td>
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receiving MT is 20% to 65%\textsuperscript{53,120–121} but instituting MTPs has decreased mortality rates by more than 50%.\textsuperscript{53,106,122,123} There are, however, side effects and risks associated with blood transfusions. Therefore, DCR should be reserved for patients who are in hemorrhagic shock or will require an MT.\textsuperscript{124} The problem is determining which patients will eventually require an MT and which will not.

During WWII, Beecher\textsuperscript{11} used increasing pulse, decreasing blood pressure, and cool skin as indications for a blood transfusion.\textsuperscript{11} Based on this and experiences from previous wars,\textsuperscript{8} the US military showed that a patient’s baseline mental status (assuming no head injury)\textsuperscript{125} and a normal radial pulse\textsuperscript{126} could be used to reliability predict the need for transfusion and a life-saving intervention.\textsuperscript{127} When ultrasound is available, the ABC Score is able to predict the need for an MT based on a scoring system that gives points for penetrating mechanism, positive focused assessment sonography for trauma, systolic blood pressure less than or equal to 90 mm Hg, and an arrival heart rate greater than 120 beats per minute.\textsuperscript{128} This scoring system was verified in a rural hospital\textsuperscript{129} and in a multicenter trial.\textsuperscript{130} It is currently being used in civilian medical transport helicopters to determine if blood products should be given in the prehospital setting.\textsuperscript{131} Although it has a tendency to overactivate the MTP, it misses less than 5% of MT or substantial bleeding scenarios.\textsuperscript{130}

**Viscoelastic Hemostatic Assays**

Thrombelastography (TEG) was developed almost 70 years ago\textsuperscript{132} to evaluate clot initiation, formation, strength, stability, and breakdown\textsuperscript{57,133} in addition to evaluating the patient for hypocoagulable and hypercoagulable states.\textsuperscript{134,135} It was not used to guide therapy for trauma patients until half a century later when it was shown to be easier to use, more cost efficient, and a better prognosticator of blood transfusion than conventional coagulation tests (CCT)\textsuperscript{132,136} because it is able to evaluate the entire coagulation cascade\textsuperscript{133} rather than just plasma.\textsuperscript{134} There are two commercially available viscoelastic hemostatic assays (VHA): TEG and rotational thromboelastometry. Both use whole blood and rotation, but TEG rotates a cup with a fixed metal piston suspended in the blood sample, whereas rotational thromboelastometry rotates a metal pin in a blood sample contained in a stationary cup.\textsuperscript{137} Rapid TEG (r-TEG) introduces tissue factor as an additional activator\textsuperscript{138} and is thus able to provide initial results to guide resuscitation within 5 minutes, an almost 10-fold improvement over CCT and traditional TEG.\textsuperscript{139} A series of retrospective trials demonstrate the superiority of VHA to CCT.\textsuperscript{135,140,141} More recently, the Denver group noted improved survival for MTP patients that were randomized to resuscitation with VHA versus CCT.\textsuperscript{142} In addition, r-TEG-guided resuscitation resulted in decreased transfusions of plasma, platelet, and cryoprecipitate compared with CCT. Both the Denver and Houston groups have published recommended treatment thresholds for r-TEG (Table 2).

**Hemostatic Adjuncts**

In addition to describing clot formation, VHA also provides information on fibrinolysis, or clot breakdown, that is not afforded by CCT. Posttraumatic fibrinolysis is a spectrum with excessive clot breakdown resulting in uncontrolled bleeding to one extreme and shutdown resulting in thrombus formation and subsequent organ dysfunction to the other.\textsuperscript{143} Both extremes are associated with increased mortality and are diagnosed based on TEG LY30. Hyperfibrinolysis is a highly lethal state, commonly present on the verge of exsanguination,\textsuperscript{143} for which mortality increases significantly with each percentage increase in LY30.\textsuperscript{64} It is treated with tranexamic acid, a synthetic antifibrinolytic derivative that blocks plasminogen from binding with fibrin and thus inhibits dissolution of the fibrin clot.\textsuperscript{144} Tranexamic acid is administered in the first
3 hours after injury to patients with LY30 values greater than 3%, the percentage at which mortality increases significantly, without increasing mortality. Other hemostatic adjuncts for bleeding patients include prothrombin complex concentrate and recombinant activated factor VII.

Avoiding Hypothermia

In addition to providing the proper resuscitation fluid, it is also important to limit other causes of coagulopathy and blood loss by correcting hypothermia, not causing unnecessarily high blood pressure, and stopping surgical bleeding. Severely injured trauma patients are frequently hypothermic because of exposure and infusion of cold fluids. This worsens coagulopathy and increases mortality because of decreased fibrinogen synthesis and reduced platelet function. As a result, it is necessary to implement warming techniques, including warmed intravenous fluids and heating blankets, to patients with hypothermia.

SUMMARY

The current practice of hypovolemic shock resuscitation for trauma is similar to the protocols developed while treating thousands of severely injured soldiers during WWI and WWII. Deviation from these practices in the second half of the twentieth century has been rejected based on experiences and trials conducted over the last decade. Continued expansion of DCR into civilian practice will result in some changes, but it is hoped not to the point that inferior care is provided and clinicians are not forced to relearn the same lessons in the future.

REFERENCES

2. Blundell J. Some account of a case of obstinate vomiting, in which an attempt was made to prolong life by the injection of blood into the veins. Med Chir Trans 1819;10(Pt 2):296–311.

Table 2

<table>
<thead>
<tr>
<th>r-TEG Parameter</th>
<th>Interpretation</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>ACT ≥128 s</td>
<td>Prolonged with factor deficiency, severe hemodilution</td>
<td>Plasma</td>
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<tr>
<td>K-time ≥2.5 min</td>
<td>Increased with hypofibrinogenemia ± platelet dysfunction</td>
<td>Plasma ± cryoprecipitate</td>
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<tr>
<td>z-angle ≤65°</td>
<td>Decreased with hypofibrinogenemia or platelet dysfunction</td>
<td>Cryoprecipitate (or fibrinogen concentrate)</td>
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<tr>
<td>MA ≤55 mm</td>
<td>Decreased with platelet dysfunction ± hypofibrinogenemia</td>
<td>Platelets ± cryoprecipitate</td>
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<tr>
<td>LY-30 ≥3%</td>
<td>Increased with accelerated fibrinolysis</td>
<td>Tranexamic acid or aminocaproic acid</td>
</tr>
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Abbreviations: ACT, activated clotting time; LY-30, lysis 30 min after MA greater than 20 mm; MA, maximal amplitude.


65. Ley EJ, Clond MA, Srour MK, et al. Emergency department crystalloid resuscitation of 1.5 L or more is associated with increased mortality in elderly and non-elderly trauma patients. J Trauma 2011;70:398–400.


