Novel concepts for damage control resuscitation in trauma

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Purpose of review
Traumatic injuries are a major cause of mortality worldwide. Damage control resuscitation or balanced transfusion of plasma, platelets, and red blood cells for the management of exsanguinating hemorrhage after trauma has become the standard of care. We review the literature regarding the use of alternatives to achieve the desired 1 : 1:1 ratio as availability of plasma and platelets can be problematic in some environments.

Recent findings
Liquid and freeze dried plasma (FDP) are logistically easier to use and may be superior to fresh frozen plasma. Cold storage platelets (CSPs) have improved hemostatic properties and resistance to bacterial contamination. Low titer type O whole blood can be transfused safely in civilian patients.

Summary
In the face of hemorrhagic shock from traumatic injury, resuscitation should be initiated with 1 : 1 : 1 transfusion of plasma, platelets, and red blood cells with limited to no use of crystalloids. Availability of plasma and platelets is limited in some environments. In these situations, the use of low titer type O whole blood, thawed or liquid plasma, cold stored platelets or reconstituted FDP can be used as substitutes to achieve optimal transfusion ratios. The hemostatic properties of CSPs may be superior to room temperature platelets.

Keywords
cold storage platelets, damage control resuscitation, freeze dried plasma, liquid plasma, thawed plasma, whole blood

INTRODUCTION

Traumatic injury is the leading cause of death among persons aged 1–44 in the United States [1]. Exsanguinating hemorrhage is the most preventable cause of death from trauma in both the civilian and military patients [2–6]. The collective experience from treating injured warfighters over the past two decades has changed initial treatment of hemorrhagic shock historically promulgated by Advanced Trauma Life Support guidelines. Borgman *et al.* [7] showed in their retrospective analysis of injured warfighters treated in Iraq, those receiving high ratio transfusions of plasma to RBC were more likely to survive. A similar association of improved survival with increased plasma and platelet to RBC ratios in the civilian trauma population was then reported by Holcomb *et al.* [8]. Encouraged by these experiences, initial resuscitation of trauma patients has moved away from large volume crystalloids and primarily RBC transfusion to the use of 1 : 1 : 1 [1 unit plasma: 1 unit platelet: 1 unit packed RBC (PRBC)] transfusion. The use of high ratio transfusion of blood components is termed hemostatic resuscitation. Hemostatic resuscitation combined with a heightened focus on early control of bleeding is known as damage control resuscitation (DCR) [9]. DCR is now considered the optimal strategy for managing exsanguinating trauma patients [10,11]. However, in resource limited environments (e.g., small community hospitals and austere locations),

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KEY POINTS

- Balanced 1 : 1:1 plasma:platelet:RBC transfusion is desired, but whole blood is superior.
- FDP is logistically simpler to use and is equivalent to traditional plasma.
- CSP may not stay in circulation as long as room temperature platelets, but have improved aggregation response and lower risk for bacterial contamination.

achieving a 1 : 1 : 1 ratio may be difficult and alternatives to fresh frozen plasma (FFP) and room temperature platelets are available.

DAMAGE CONTROL RESUSCITATION

A large multicenter prospective observational study was undertaken to confirm the findings of multiple retrospective DCR studies. This study included 1245 patients from 10 level one trauma centers and concluded that blood product ratios varied significantly during the time of resuscitation, but increased platelet to PRBC and plasma to PRBC ratios were associated with decreased mortality at 6 h [12]. As a follow up to the observational trial, a prospective randomized trial comparing 1 : 1:1 ratios of plasma: platelet: PRBC with 1 : 1:2 was undertaken in 680 patients [13]. This study concluded that the 1 : 1:1 group had a significantly lower risk of death from exsanguination at 24 h. The recently published Eastern Association for the Surgery of Trauma (EAST) practice management guideline [14▪] recommends DCR as the standard of care. Maintaining a 1 : 1:1 transfusion ratio is important, but equally important during DCR is the avoidance of hypothermia, minimization of blood loss with hemorrhage control (direct pressure, hemostatic dressings, and tourniquet application), hypotensive resuscitation, limiting use of crystalloids, massive transfusion protocol (MTP) to ensure adequate blood product availability, expeditious definitive surgical and/or angiographic control of hemorrhage, administration of pharmacologic adjuncts (e.g., tranexamic acid), and the use of viscoelastic assays (e.g., thrombelastography) to guide ongoing transfusions. This hemorrhage control bundle of care has been associated with decreased death from hemorrhage and an overall improvement in outcome [6].

FRESH FROZEN, THAWED, LIQUID, AND FREEZE DRIED PLASMA

Despite having a MTP in place, it may be difficult for exsanguinating patients to receive plasma within minutes of injury. In the majority of hospitals and far forward military surgical teams, FFP is used as the primary resuscitation fluid. Although FFP can be stored for up to 1 year, it is logistically difficult to use because it requires storage at –18°C and a lead time of up to 30 min or more to thaw before use. This is problematic with an exsanguinating patient requiring immediate massive transfusion. In these situations, recent studies document that every minute really does make a difference in survival [15]. Thawed plasma, FFP which is prethawed and stored at 1–6°C for up to 5 days, can be available for DCR without delay. While having readily available thawed plasma on hand for use in busy tertiary hospitals is beneficial, smaller institutions may be concerned about increasing waste [16]. However, Wehrli [17] *et al.* document an actual saving with their study comparing plasma wastage 1 year before versus 1 year after implantation of thawed plasma. Another alternative is liquid plasma (LQP), or never frozen plasma, which can be stored at 1–6°C for up to 26 days in citrate phosphate dextrose (CPD) or 40 days in citrate phosphate dextrose adenine (CPDA-1). When comparing the efficacy of thawed plasma to LQP, studies to date have mixed results. Matijevic *et al.* [16] conclude that LQP is superior to thawed plasma with increased thrombin generation, capacity, and ability to form clot rapidly. However, by day 26, LQP was no different from thawed plasma on day 5. Backholer *et al.* [18▪▪] show equivalence in hemostatic variables between thawed plasma and LQP for up to 7 days of storage. However, when comparing LQP on day 11 with day 5, factors II, V, VII, and protein S activity were lower. They recommend a shelf life of less than 14 days for LQP. In summary, never frozen LQP provides superior shelf life compared to thawed plasma or FFP.

Freeze dried (lyophilized) plasma (FDP) is another alternative plasma product that can be used in DCR to achieve the desired transfusion ratios. FDP is stored at room temperature and can be reconstituted and ready for transfusion within minutes. The use of FDP to treat hemorrhage is not a new concept, as the US Army transfused hundreds of thousands of units of FDP during World War II. In order to produce large amounts of FDP, plasma from more than 1000 donors was pooled [19▪]. However, FDP production was halted in 1968 because of the risk of pathogen transmission, especially hepatitis [20]. The German Red Cross Blood Service West (Hagen, Germany) developed both solvent detergent-treated lyophilized pooled plasma and single donor FDP [20]. The pooled lyophilized plasma was abandoned because of the inability to inactivate prions with solvent detergent treatment. LyoPlas N-w is the single donor FDP product which has been licensed since 2007 in Germany, and has a shelf life of 15 months when stored at 2–25°C. It is recommended to be transfused within 6 h of reconstitution.

Frozen plasma is thawed and lyophilized into FDP only when the donor is confirmed to be negative for HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV). The lyophilization process results in only a minimal activity reduction of factors V, XI, protein S, and VWF, and 15% loss of factor VIII activity. LyoPlas N-w is fully approved in Germany for transfusion and between 2007 and 2011, over 230 000 units were transfused without adverse reactions or reported virus transmission. Both the Israeli Defense Force Medical Corps and Norwegian Hospital Emergency Medical Servicehave used LyoPlas N-w with success in the prehospital environment at the point of injury.

The French have been producing FDP since 1945, and it was used extensively during the Indochina War [21]. There was a brief pause in use from 1985 to 1991 because of concerns for HIV transmission. However, FDP production restarted at the beginning of the first Persian Gulf War. French FDP (FLYP) is made from FFP pooled from 11 or less individuals by apheresis. It is tested for HIV, HBV, HCV, human T-cell leukemia, syphilis, Chagas, and malaria antibodies. FLYP is leukoreduced with DNA and RNA pathogens, inactivated by ultraviolet light and chemically with amotosalen. Since 2011, FLYP has been authorized by the French government for civilian use in austere environments and when thawed plasma is not available. Plasma is collected, treated, and then frozen. The plasma is then thawed, pooled, and lyophilized. The lyophilization process only decreases factors V and VIII. FLYP can be stored at room temperature for 2 years and is reconstituted in less than 6 min. It is ABO universal and since 1994, over 1000 units have been transfused without adverse effects or infections. At this time, no FDP product is approved for use in the United States. Under a US Food and Drug Administration Investigational New Drug protocol, there is limited use of FDP by selected US Special Operations Forces [19▪,22▪]. There are several companies developing FDP for use in the United States [22▪].

ROOM TEMPERATURE AND COLD STORAGE PLATELETS

Current blood bank recommendations state that platelets should be stored at room temperature (22 °C), under constant agitation, with a shelf life of 5 days. These current storage requirements are not optimized for hemostatic function or safety, but to maximize survival *in vivo* following transfusion for those with hypoproliferative thrombocytopenia, not bleeding patients who need platelets for clot initiation after trauma [23]. Room temperature platelets are approved for use for only 5 days because of the increasing risk of bacterial contamination. Cold storage platelets (CSPs) are kept at 1–6°C and when placed in platelet additive solution or plasma, can retain their function for up to 15 days [24▪]. Studies from the 1970s show that CSPs have a better aggregation response and adhesion to the subendothelium, as well as reducing bleeding times in thrombocytopenic patients, those taking aspirin, and aplastic thrombocytopenic patients [25]. More recently, Reddoch *et al.* [25] performed an in-vitro comparison of apheresis platelets stored at 4 and 22°C. They concluded that CSPs are superior to room temperature platelets with superior bacteriologic safety, aggregation response, clot strength, and release of fewer proinflammatory mediators.

WHOLE BLOOD

The use of whole blood for the initial treatment of hemorrhagic shock is not a new concept. Prior to the introduction of blood component therapy in 1965, whole blood was the product of choice for resuscitation in the military. During World War II, almost all US Army combat casualties received type O whole blood. Over 400 000 units of cold storage whole blood were given during the Korean War [26] and more than one million units during the Vietnam War [27]. Component therapy with FFP, PRBC, and platelets for resuscitation of hemorrhagic shock supplanted whole blood transfusion by the 1970s. As discussed previously, with the recent experience in treating combat casualties in Afghanistan and Iraq, DCR with 1 : 1:1 transfusion ratios of plasma: platelets: PRBC has emerged as the standard of care. However, in austere and far forward military environments or community hospitals with limited access to plasma or platelets, DCR may not be possible. Even with a perfect 1 : 1:1 ratio mixture of plasma: platelets: PRBC, the hemoglobin concentration is 9 g per deciliter, the platelet count is 88 000/μl, there is 750 mg of fibrinogen, and 65% coagulation factor activity. In summary, without a single drop of clear fluid (crystalloid or artificial colloids), a 1 : 1:1 ratio delivers an anemic, thrombocytopenic, and coagulopathic solution.

In comparison, a 500-ml unit of whole blood has a hemoglobin concentration of 13–14 g per deciliter, 150 000–400 000 platelets/μl, 1500 mg of fibrinogen, and nearly 100% activity of clotting factors [28▪]. Not only does the use of whole blood allow the medical team to easily achieve the desired DCR ratio, but it also provides optimal volume resuscitation, hemostatic function, and oxygen carrying capacity compared to reconstituted blood from components. In the deployed military setting, whole blood is obtained from soldiers in the immediate area, otherwise known as the 'walking blood

bank'. All US military personnel are routinely tested prior to deployment for HIV, hepatitis, and syphilis and are vaccinated for hepatitis A virus and HBV. All recipients of whole blood are tested for transfusion transmitted diseases at 3, 6, and 12-month intervals post transfusion in order to monitor for possible disease transmission [29▪]. Although recent tradition calls for type-specific whole blood, low titer anti-A and anti-B type O whole blood (LTOWB) can be collected from Armed Services Blood Program donor centers or walking blood banks and stored refrigerated for 21 days in CPD or 35 days in CPDA-1 [30,31]. Several in-vitro studies have shown that LTOWB retains its coagulation function over period of 14–21 days [31–33]. The use of whole blood in the military setting is independently associated with improved survival [34,35].

The use of whole blood has been limited in the civilian population because of concerns over acute hemolytic transfusion reactions and the theoretical reduction in hemostatic properties of CSP [36▪▪]. In the military setting, the blood type of the injured warfighter is usually already known and most will receive TSWB which greatly decreases the risk of an acute hemolytic transfusion reaction. When treating civilian trauma patients during the initial phase of DCR (prehospital and hospital), the blood type is unknown and type O whole blood must be used. One unit of type O whole blood contains approximately 250 ml of plasma which contains both anti-A and anti-B antibodies. If transfused into a nontype O recipient, an acute hemolytic reaction may occur resulting in disseminated intravascular coagulopathy and rarely death. However, transfusion of LTOWB from type O donors lowers the risk of a transfusion reaction [37]. The problem is the lack of agreement and standardization on what is considered to be 'low titer'. The Norwegian military and Swedish Special Forces both use cold storage LTOWB with titers less than 400 (IgG method) and less than 100 (IgM method) [30,38,39]. The 75th Ranger Regiment, US Army Special Operations Command, allows for the use of LTOWB with IgM titers less than 256 [40]. Yazer *et al.* [41▪▪] compared 47 patients who received up to two units of cold storage leukoreduced LTOWB with a retrospective cohort of 145 patients receiving blood component therapy. Although the use of LTOWB was not associated with an improvement in mortality, the study showed no significant increases in the levels of haptoglobin after transfusion of LTOWB, suggesting that no acute hemolytic reactions occurred. Cotton *et al.* [42] performed a single center prospective randomized trial comparing 55 patients who received modified whole blood and platelets with 52 patients receiving 1 : 1:1 component therapy. The primary outcome showed no difference in the transfusion volumes over the first 24 h. In this study, however, the modified whole blood was cold stored, leukoreduced, and platelet depleted, therefore it required addition of room temperature apheresis or pooled platelets to achieve the 1 : 1:1 DCR ratios. Other limitations to the study were the unequal inclusion of severe traumatic brain injury patients with potential nonsurvivable injuries and the use of TSWB and not LTOWB. The initial use of LTOWB is now starting to be used at multiple civilian trauma centers around the United States to treat civilian trauma patients in hemorrhagic shock [43▪▪].

CONCLUSION

The benefits of DCR with a 1 : 1:1 transfusion ratio in resuscitation of bleeding trauma patients have been established in numerous studies. However, achieving the goal ratio during resuscitation may be problematic in small community hospitals or austere environments. Logistically simpler compared to FFP, thawed plasma and LQP can be stored at refrigerated temperatures and can be transfused with minimal delay. Even simpler, is the use of FDP, which can be stored in a wide range of temperatures, and can be reconstituted quickly. The use of cold stored LTOWB appears promising, as ratios are 'preachieved', the platelets within have superior aggregation response, and with low anti-A and anti-B antibodies, the risk of acute hemolytic transfusion reaction is low. Ideally, in order of preference and depending on the availability of cold chain storage, trauma patients with exsanguinating hemorrhage should receive: FDP, LTOWB, TSWB, 1 : 1:1 FDP:CSP:PRBC, 1 : 1 FDP:PRBC, or lastly just RBCs. Ironically, these 'novel' concepts in DCR are not new at all, they have merely just been rediscovered.

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Conflicts of interest

There are no conflicts of interest.

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