Prehospital Resuscitation

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Introduction

While resuscitation of the injured patient has evolved substantially over the last two decades, only recently has it been recognized that prehospital resuscitation can have a significant impact on outcomes. There has been a focus on damage control resuscitation in the hospital-based setting, providing nearly equal ratios of packed red blood cells (PRBC), plasma, and platelets to not only replace oxygen-carrying capacity but also treat trauma-induced coagulopathy (TIC) [1, 2]. However, evidence demonstrates markers of a pro-inflammatory response and coagulopathy are present within minutes of injury at the scene [3, 4]. Thus, the type and volume of fluid that a severely injured patient receives or does not receive in the prehospital setting can set them on a trajectory toward a good or poor outcome.

While initially TIC was thought to be due to dilutional effects of crystalloid, recent work has demonstrated TIC develops with tissue injury and shock independent of resuscitation, shifting the focus toward directly addressing this TIC by restoring coagulation factors and limiting dilutional and pro-inflammatory effects from crystalloid that impair coagulation [5, 6]. Crystalloid remains the de facto resuscitation fluid in the field; however, prehospital blood product resuscitation is becoming more common [7]. This has led to a push to extend damage control resuscitation principles into the field for severely injured patients in hemorrhagic shock.

Resuscitation Access in the Field

Intravenous Access

Prehospital resuscitation begins with obtaining intravenous (IV) access in the field. Because flow rate is directly proportional to the inner cannula diameter and inversely proportional to the length of the catheter, short large-bore IVs are ideal in the bleeding trauma patient. This can be readily achieved with insertion of 16-gauge peripheral IVs. Intravenous access falls within the scope of practice for advanced life support (ALS) providers (i.e., paramedics and advanced emergency medical technicians as well as prehospital flight nurses and advance practice providers). Attempts at peripheral access can prolong prehospital time up to 12 minutes, particularly with failed attempts [8–10]. Thus, transport should not be delayed for attempts at IV access, instead favoring access obtained en route. Current guidelines recommend only two attempts at peripheral IV access prior to moving on to another access modality [11].

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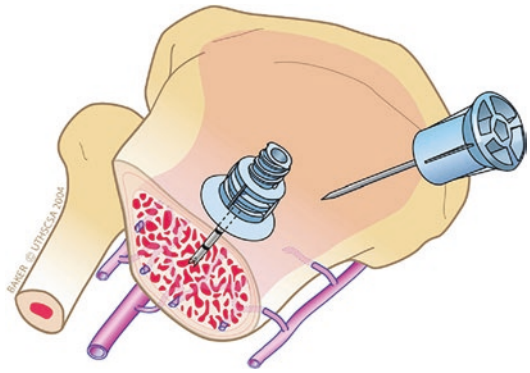

Fig. 29.1 Intraosseous access in the proximal tibia. (Reprinted with permission from Smart et al. [14])

Central venous access is rarely used in the US prehospital system but more commonly performed in European prehospital systems where physicians are routinely providing field care [12]. Some air medical services have the ability to insert central venous catheters in the United States, and studies suggest percutaneous Seldinger technique is preferred for safety and speed of access over cut-down methods [13].

Intraosseous Access

Intraosseous (IO) access has become the favored second-line access modality in most US prehospital systems, owing to its technical ease and speed of insertion with automated drills (Fig. 29.1) [15]. IO placement is commonly performed in the proximal tibia, humeral head, or occasionally the sternum. Further, IO allows infusion of fluids, medications, as well as blood products. Given these characteristics, IO access is often used as first-line access for patients in extremis or cardiac arrest.

Prehospital Crystalloid

Crystalloid Physiologic Effects

Crystalloid is the de facto resuscitation fluid used in the majority of prehospital systems in the United States. Crystalloid is inexpensive, widely available, and highly durable in a range of environmental conditions. Animal experiments in the 1960s and 1970s suggested extracellular fluid compartment deficits that required large volumes of crystalloid to correct in hemorrhagic shock [16, 17]. These findings led to the 3:1 rule of replacement with at least threefold greater volume of crystalloid than estimated blood loss and promulgation of the initial 2 l bolus of crystalloid for prehospital providers.

Subsequent investigation elucidated significant deleterious effects of crystalloid resuscitation, especially in large volumes. Saline in particular can cause metabolic hyperchloremic acidosis which in turn leads to dysregulation of the coagulation cascade enzymes at suboptimal pH levels with impaired thrombin generation. Acidosis from large volumes of saline can also impair cardiac contractility as well as the effectiveness of circulating catecholamines to effect compensatory vasoconstriction [18].

Further, crystalloid fluids incite a pro-inflammatory state with activation of neutrophils, increase neutrophil adhesion, and promote release of tumor necrosis factor-alpha, interleukin (IL)-6, IL-8, and IL-10 leading to intracellular edema and dysfunction, as well as vasodilation and capillary leak [19, 20]. Prehospital crystalloid volume has also been associated with hyperfibrinolysis in some patients, a highly lethal phenotype [21]. Dilutional effects on the coagulation proteins due to crystalloid infusion occur and contribute to clinical coagulopathic bleeding, although they are distinct from the pro-inflammatory effects promoting ongoing coagulopathy in injured patients [5, 18, 19, 22]. These detrimental effects have been borne out in clinical studies demonstrating increased mortality associated with greater volumes of prehospital crystalloid administration [21, 23–25].

Several groups investigated hypertonic saline as a potential prehospital resuscitation fluid, with early promising results [26–29]. Hypertonic saline was hypothesized to have a more favorable physiologic profile as it required a lower volume of fluid to restore intravascular volume and had less pro-inflammatory effects [30–33]. Two large prehospital resuscitation trials were conducted using hypertonic saline compared to isotonic crystalloid [34, 35]. One was performed in

patients with traumatic brain injury (TBI) and one in patients in hemorrhagic shock; however, both were stopped early for futility (Table 29.1). Thus, hypertonic saline has not found use in prehospital resuscitation protocols in the United States.

Prehospital Crystalloid Volume

Given these findings, current practice has moved away from prehospital and early in-hospital resuscitation with large volumes of crystalloid. The landmark trial by Bickell et al. was one of the first to demonstrate withholding crystalloid infusion for patients with penetrating torso trauma until definitive hemorrhage control was achieved significantly improved survival to discharge (Table 29.1) [36]. However, not all studies have reported worse outcomes associated with higher prehospital crystalloid volume, and some have reported improved survival particularly in patients with TBI [37, 48–53]. The question of optimal prehospital crystalloid volume among different patient populations remains. This continues to be an important question, as crystalloid will continue to be the primary prehospital resus-

Table 29.1 Selected randomized prehospital trauma resuscitation trials

Trial	Published	Design and methods	Main result
Bickel et al. [36]	1994	Single-center, randomized patients with penetrating torso injury and SBP <90 to receive immediate crystalloid resuscitation or no crystalloid until surgical control of hemorrhage	8% reduction of in-hospital mortality in delayed fluid group (n = 309) compared to immediate fluid group (n = 289) 30% vs. 38%, p = 0.04
Turner et al. [37]	2000	Multicenter, cluster randomized paramedics (n = 401) to standard crystalloid resuscitation (500 mL bolus with additional crystalloid for signs of shock at paramedic discretion) or no crystalloid resuscitation in trauma patients; paramedics cross over to other resuscitation protocol at trial half completed point	No difference in 6-month mortality in no crystalloid group (n = 699) compared to standard resuscitation group (n = 610) 9.8% vs. 10.4%, p = 0.72
HTS TBI [34]	2010	Multicenter, blinded, randomized patients with GCS <8 and without shock criteria (see HTS shock below) to receive 250 mL of 7.5% HTS + dextran, 7.5% HTS, or normal saline	No difference in 6-month proportion of patients with Glasgow Outcome Scale-Extended ≤4 in HTS + dextran group (n = 359) compared to HTS group (n = 341) or saline group (n = 582) 54% vs. 54% vs. 52%, p = 0.67
HTS Shock [35]	2011	Multicenter, blinded, randomized patients with severe hypotension (SBP <70) or hypotension and tachycardia (SBP 71–90 + HR ≥ 108) to receive 250 mL of 7.5% HTS + dextran, 7.5% HTS, or normal saline	No difference in 28-day mortality in HTS + dextran group (n = 231) compared to HTS group (n = 269) or saline group (n = 395) 25% vs. 27% vs. 25%, p = 0.91
ROC Hyporesus [38]	2015	Multicenter, randomized patients with hypotension (SBP <90) and GCS >8 to controlled resuscitation (250 mL boluses for SBP <70 or non-palpable radial pulse) or standard resuscitation (2000 mL bolus with additional crystalloid to keep SBP >110)	Lower unadjusted 24-hour mortality in controlled resuscitation group (n = 97) compared to standard resuscitation group (n = 95), but no difference in risk-adjusted mortality (p > 0.05) 5% vs. 15%, p = 0.03
PAMPer [39]	2018	Multicenter, cluster randomized helicopter bases (n = 27) to administration of two units of plasma or standard resuscitation in patients with severe hypotension (SBP <70) or hypotension and tachycardia (SBP 71–90 + HR ≥ 108)	10% reduction of 30-day mortality in plasma group (n = 230) compared to standard resuscitation group (n = 271) 23% vs. 33%, p = 0.03

(continued)

Table 29.1 (continued)

Trial	Published	Design and methods	Main result
COMBAT [40]	2018	Single center, randomized patients with severe hypotension (SBP <70) or hypotension and tachycardia (SBP 71–90 + HR ≥ 108) to receive two units of plasma or standard resuscitation with saline	No difference in 28-day mortality in plasma group ($n = 65$) compared to standard resuscitation group ($n = 60$) 15% vs. 10%, $p = 0.37$
RePHILL [41]	Recruiting	Multicenter, randomized patients with hypotension (SBP <90 or absent radial pulse) to receive prehospital blood product resuscitation (up to two units of PRBC and two units of freeze-dried plasma) or crystalloid resuscitation (up to four 250 mL normal saline boluses). Primary outcome is composite of in-hospital mortality and failure of lactate clearance ≥20% 2 hours after randomization. Enrollment goal of 490 patients	Pending
STAAMP [42]	Recruiting	Multicenter, blinded, randomized patients with SBP <90 or HR >110 within 2 hours of injury to receive 1gm bolus tranexamic acid or placebo. Primary outcome is 30-day mortality. Enrollment goal of 994 patients	Pending
PATCH [43]	Recruiting	Multicenter, blinded, randomized patients with prehospital Coagulopathy of Severe Trauma (COAST) score ≥3 within 3 hours of injury to receive 1gm bolus tranexamic acid or placebo. Primary outcome is 6-month mortality and Glasgow Outcome Scale-Extended. Enrollment goal of 1184 patients	Pending
TXA in TBI [44]	Completed	Multicenter, blinded, three-arm trial randomizing patients with GCS <13 to receive 1 gm tranexamic acid, or 2 gm tranexamic acid, or placebo. Primary outcome is 6-month Glasgow Outcome Scale-Extended. Enrolled 967 patients	Pending
FlinTIC [45]	Recruiting	Single-center, blinded, randomized patients with visible hemorrhage or clinical signs of bleeding to receive 50 mg/kg of fibrinogen concentrate or placebo. Primary outcome is fibrinogen polymerization. Enrollment goal of 60 patients	Pending
PPOWER [46]	Recruiting	Single-center, randomized patients with severe hypotension (SBP <70) or hypotension and tachycardia (SBP 71–90 + HR ≥ 108) to receive two units of whole blood or standard resuscitation. Primary outcome is 28-day mortality. Enrollment goal of 112 patients.	Pending
PREHO-PLYO [47]	Recruiting	Multicenter, randomized patients with severe hypotension (SBP <70) or Shock Index >1.1 to receive freeze-dried plasma or normal saline resuscitation. Primary outcome is INR change from prehospital to admission. Enrollment goal of 140 patients	Pending

SBP systolic blood pressure, *mL* milliliters, *GCS* Glasgow Coma Scale, *HTS* hypertonic saline, *TBI* traumatic brain injury, *HR* heart rate, *PRBC* packed red blood cells

citation fluid for the foreseeable future in the vast majority of ground emergency medical service systems, despite advances in prehospital transfusion and resuscitation.

There is some evidence that patients with hypotension in the field benefit from crystalloid administration. Hampton and colleagues demonstrated that a 16% reduction in the hazard of mor-

tality was independently associated with a median infusion of 700 mL of prehospital crystalloid among patients requiring early blood transfusion upon arrival to the trauma center [54]. Another retrospective review of severely injured blunt trauma patients compared high (>500 mL) versus low volume of prehospital crystalloid stratified by prehospital hypotension. Patients without hypotension have a nearly 2.5-fold increase in mortality if receiving >500 mL of prehospital crystalloid; however, there was no increase in mortality for hypotensive patients [48]. Further, the highest mortality among hypotensive patients was among those receiving no prehospital crystalloid. A recent secondary analysis of the Prehospital Air Medical Plasma (PAMPer) trial demonstrated similar findings, with the highest mortality among severely hypotensive patients (systolic blood pressure <70 mmHg) receiving no prehospital crystalloid but the lowest mortality among patients receiving 1–500 mL when crystalloid was the only available prehospital resuscitation fluid [55]. The Resuscitation Outcomes Consortium conducted a pilot study that randomized patients with hypotension in the field to receive a 2 l crystalloid bolus plus fluid to maintain a systolic blood pressure >110 mmHg or receive 250 mL boluses only when systolic blood pressure was <70 mmHg or non-palpable radial pulse (Table 29.1) [38]. The group found the controlled bolus strategy resulted in a lower volume of prehospital crystalloid (average 1 l compared to 2 l) with lower unadjusted 24-hour mortality, but not adjusted mortality. This effect was predominantly in blunt trauma patients.

The harmful effects of hypotension in the field on outcome in patients with TBI are well documented, with a doubling of mortality for even a single episode of prehospital hypotension [56]. One evaluation of lowest field systolic blood pressure demonstrated an inverse relationship between survival and systolic blood pressure between 40 and 120 mmHg, suggesting no specific threshold abates the mortality associated with secondary insult in TBI [57]. Current guidelines recommend fluid therapy in the prehospital setting to maintain a systolic blood pressure >90 mmHg to prevent secondary insult, despite no direct evidence that raising the blood pressure improves survival or functional outcome [11]. One recent study demonstrated that implementation of prehospital TBI management guidelines was associated with more crystalloid boluses given, less hypotension on arrival to the trauma center, and reduced mortality in severe TBI patients [53].

Given current evidence, when crystalloid is the only prehospital fluid available to prehospital providers, very limited (<500 cc) or no crystalloid should be provided to non-hypotensive patients. Severely hypotensive patients may still benefit from small amounts of crystalloid, with 250 mL boluses targeting a systolic blood pressure of 70–80 mmHg, palpable radial pulse, or normal mental status, especially in blunt trauma without TBI. Providers should aim for a total volume of 500 mL to a maximum of 1 l. Patients with penetrating torso trauma should receive limited or no prehospital fluid, and prehospital access/resuscitation attempts should not delay transport to a trauma center. Finally, in the absence of additional evidence, patients with suspected TBI should receive crystalloid boluses targeting a systolic blood pressure >90 mmHg.

Prehospital Blood Products

With mounting evidence of the deleterious effect of crystalloids in severely injured patients, the focus is now on damage control resuscitation with blood product component resuscitation and attention to the ratio of plasma and platelets to PRBC. The goal is to restore tissue oxygenation and a more physiologic coagulation milieu with the repletion of coagulation factors and platelets while avoiding the pro-inflammatory and dilutional coagulopathy induced from crystalloid infusion. This strategy has shifted toward earlier and higher ratio of blood product components, with a more balanced component transfusion in an attempt to approximate what is lost—whole blood. Given the success of damage control resuscitation employed early in the hospital setting [1, 2, 58, 59], it only makes sense to push

this strategy into the field to address hemorrhagic shock as early as possible. Data demonstrating death from hemorrhage occurs within the first 3 hours from injury and one-third of deaths from exsanguination occur in the field highlight the critical window for blood product administration in the prehospital setting [60, 61].

The initial experience with prehospital blood product resuscitation dates back to military medicine in World War II [62] (see Chap. 1). More recently demonstrated in Iraq and Afghanistan, prehospital blood product resuscitation has shown improved survival and has become the standard of combat casualty care when available [63–67]. Guidelines for logistics and safety of such practices in civilian prehospital trauma care have prevented widespread generalizability until lately. A survey of level 1 and 2 trauma centers participating in the Trauma Quality Improvement Program (TQIP) indicated that 34% of emergency medical services have the capability to administer prehospital blood products [7].

Packed Red Blood Cells

Packed red blood cell transfusion is the most commonly available prehospital blood product [7]. To date PRBC capabilities have generally been limited to air medical transport agencies, and early evidence has shown the practice to be both safe and feasible [68, 69]. Although prehospital PRBC transfusion has been available for decades in some areas, it is only recently that data have shown support for this practice.

The military evidence has shown improvements in mortality for patients receiving prehospital PRBC in recent conflicts. Deployment of advanced medical platforms with prehospital PRBC transfusion capabilities in the US and UK military resulted in greater than expected survival for severely injured patients [70]. Morrison et al. demonstrated that advanced prehospital capabilities including transfusion of PRBC in one-third of casualties demonstrated a 6% absolute mortality reduction among patients with injury severity score >15 [65].

The civilian evidence for the effectiveness of prehospital PRBC is mounting as well. Early studies evaluated small numbers of patients without the power to truly demonstrate effectiveness [71]. One small study of 50 propensity-matched patients receiving prehospital PRBC from the Glue Grant multicenter collaborative found a reduction in 24-hour and 30-day mortality, as well as lower risk of TIC as approximated by INR [72]. A larger single-center propensity-matched cohort of 240 air medical patients receiving prehospital PRBC after injury from the same group demonstrated that prehospital PRBC transfusion was associated with improved 24-hour mortality, lower risk of shock on arrival, and fewer PRBC required in the first 24 hours after admission [73]. A systematic review of prehospital PRBC evaluated 16 case series and 11 comparative studies [74]. The authors noted low quality of evidence with no overall effect on early or late mortality; however, they noted that studies which matched patients for severity of injury consistently suggested modest survival improvement.

Plasma

Use of prehospital plasma transfusion has gained increasing interest. Plasma has several advantages as a resuscitation fluid. Like PRBC, plasma is iso-osmolar with circulating blood and thus is an ideal fluid expander. Unlike PRBC, however, plasma contains the clotting proteins to directly address the TIC that occurs early in patients with tissue injury and hemorrhagic shock [40]. Finally, there is increasing evidence that endothelial glycocalyx degradation results in coagulopathy and endothelial dysfunction in hemorrhagic shock [75, 76]. In preclinical data, plasma has been shown to attenuate the disruption of the endothelial glycocalyx, improving outcome [77, 78].

As prehospital PRBC have long been available, few studies evaluate the sole effect of prehospital plasma resuscitation for trauma. The Mayo Clinic transport program added plasma transfusion capabilities in 2011 and reported the first five patients receiving plasma only with TBI

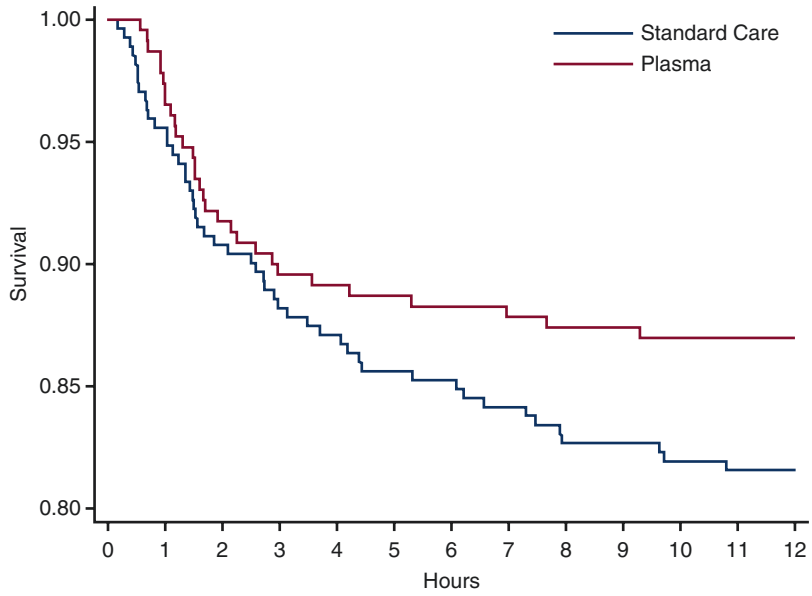

Fig. 29.2 Kaplan-Meier survival curve in the first 12 hours of patients receiving plasma or standard care resuscitation in the Prehospital Air Medical Plasma (PAMPer) trial

on warfarin for reversal [79]. All patients survived more than 24 hours and had a mean decrease of 1.2 in INR upon arrival at the trauma center. The same group updated their results in patients with TBI, comparing 36 patients receiving prehospital plasma to 40 patients receiving prehospital PRBC [80]. They found significantly improved neurologic outcomes at 6 months with higher functioning and lower disability among the prehospital plasma group.

With the promising results of preclinical and early clinical prehospital plasma data, the US Department of Defense issued a program announcement to evaluate prehospital plasma resuscitation for hemorrhagic shock in the civilian population. Ultimately two randomized trials were funded and completed, the PAMPer trial and the Control Of Major Bleeding After Trauma (COMBAT) trial (Table 29.1) [81, 82]. The multicenter PAMPer trial used a cluster randomized design by helicopter base to randomize air medical patients with severe hypotension or hypotension plus tachycardia to receive two units of thawed plasma or standard prehospital resuscitation with crystalloid or PRBC. A total of 501 patients were included and the plasma group had a 10% absolute reduction in 30-day mortality compared to the standard care arm [39]. The separation in the survival curve became evident beginning at 3 hours from injury (Fig. 29.2). There were lower 24-hour mortality, slight reduction in 24-hour transfusion requirements, and no difference in adverse events in the plasma group.

The single-center COMBAT trial randomized patients to receive thawed plasma or crystalloid in an urban ground emergency medical services system with plasma delivered upon arrival to the trauma center in both groups. A total of 125 patients were included and no difference in 24-hour or 28-day mortality was seen between the plasma or crystalloid groups [40]. When taking both trials into consideration, it becomes apparent that different populations were studied. The COMBAT trial was an urban population with median prehospital time of 26 minutes, while the PAMPer trial included air medical patients with a median prehospital time of 41 minutes. Thus, it seems early plasma transfusion is necessary, whether at the trauma center when prehospital times are short or in the prehospital setting with prolonged prehospital times.

Packed Red Blood Cells and Plasma

Following the paradigm of damage control resuscitation in the hospital setting, investigation of resuscitation with a balanced ratio of plasma and

PRBC in the prehospital setting is ongoing. Early results by Kim and colleagues in nine patients receiving prehospital PRBC and plasma compared to only PRBC suggested adding plasma resulted in greater improvement in coagulation status, higher plasma to PRBC ratio over the first 24 hours, and less crystalloid infusion [83]. As the military has added prehospital plasma capabilities to forward medical units, a retrospective matched cohort study of US combatants who experienced traumatic amputation or shock demonstrated that prehospital administration of PRBC and plasma resulted in a 15% and 12% reduction in mortality at 24 hours and 30 days, respectively [67]. Notably, of all injured patients who died, 70% where prior to hospital arrival, and of those, 74% were not transfused, again stressing the potential benefit of prehospital transfusion. A review of matched patients in the UK military experience also indicated an 11% reduction in casualties receiving prehospital PRBC and plasma transfusion [66].

Holcomb et al. reviewed their early experience of prehospital PRBC and plasma transfusion in their air medical transport program [84]. They compared 137 patients receiving PRBC and plasma to 169 controls with crystalloid only, demonstrating lower early hemorrhage rates and very early death from exsanguination in the first 6 hours, but no difference in 24-hour or 30-day mortality. A follow-up multicenter prospective study from this group compared air medical transport systems with PRBC and plasma to those without prehospital transfusion capabilities [85]. They did not find a difference in mortality; however, the data was hampered by significant differences in injury severity among patients receiving transfusion, as most systems now transfuse any severely injured patient with prehospital blood products when available. Most recently, Guyette and colleagues found that patients who received both PRBC and plasma in the PAMPer trial had the greatest survival benefit over patients receiving either PRBC or plasma alone (Fig. 29.3) [55]. A meta-analysis of prehospital transfusion suggested a pooled reduction in the odds of long-term mortality for prehospital transfusion of both PRBC and plasma, but not for PRBC alone [86].

Considering the body of evidence for improved outcomes with damage control resuscitation in the hospital setting and the more recent prehospital data, trauma patients at risk for hemorrhagic shock should be resuscitated with balanced blood product components as close to the time of injury as possible to prevent the development of coagu-

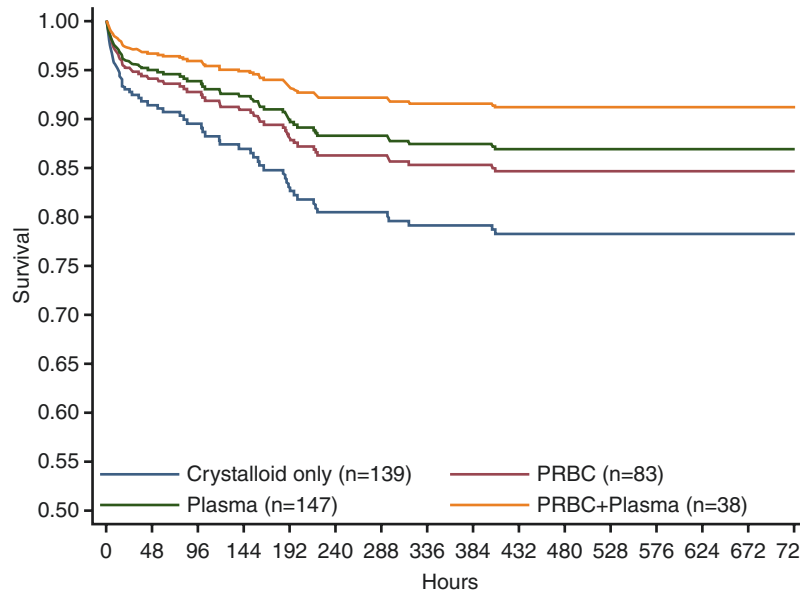

Fig. 29.3 Cox proportional hazards regression-adjusted survival curves of patients receiving crystalloid only, packed red blood cells, plasma, or packed red blood cells and plasma in the Prehospital Air Medical Plasma (PAMPer) trial

lopathy and the ensuing shock and inflammatory state associated with early mortality, most commonly within 3 hours. High ratio blood product replacement in essence reconstitutes whole blood, and current data shows the use of PRBC and plasma is feasible within modern emergency medical service transport programs [87]. The benefit of this approach is less clear in urban ground emergency medical systems with short transport times to a trauma center with damage control resuscitation capabilities.

Platelets

There is evidence that platelets are a critical component of damage control resuscitation. Evaluation of platelet transfusion has shown that higher early ratios of platelet to PRBC transfusion are associated with reduced mortality, and platelet transfusion in the PROPPR trial was associated with lower early mortality and improved hemostasis [88–90]. These data suggest early platelet transfusion in the field may be beneficial, despite limited availability of platelets in the prehospital setting [91]. At current, no studies evaluate outcomes of prehospital platelet transfusion, although the Mayo Clinical transport program recently added cold stored platelets to their prehospital transfusion capabilities [92]. Storage in the prehospital environment presents a particular challenge for platelets, but given the evidence for prehospital PRBC and plasma, cold stored platelets and whole blood storage that retains platelet function are receiving increasing interest [93–95].

Logistical Considerations

There are several challenges associated with a prehospital transfusion program. Foremost is a good working relationship with the blood bank that will be supplying products to the prehospital agency. Agencies must determine what type of products they will carry. Many agencies carry universal donor products (O negative PRBC, AB plasma); however, given the limited supply of these blood types, arguments have been made for use of low titer O positive blood and A low titer B plasma [96, 97].

There are generally two models for prehospital blood product programs. For prehospital agencies that are based at a participating hospital, blood products may be obtained "on demand" from the in-house blood banks. This model significantly decreases regulatory oversight and costs to the agency; however, it is only available to units stationed at the hospital and may prolong response time while obtaining the required blood products. When bases are located away from a participating blood bank site, base accommodations must be made to store blood products on site. Depending on local practices and regulations, it may be necessary to certify the prehospital agency bases as satellite blood banks. The agency must then purchase blood products from the blood bank at a cost of $100 to $400 per unit depending on type of blood component, blood type, and regional availability. The base must also purchase a blood refrigerator for storage (approximately $3500–$7500). Prehospital personnel then become responsible for proper storage and transport, recycling of units to prevent wastage, and documentation for the blood products (Fig. 29.4).

Fig. 29.4 Blood product storage cooler, transport cooler, and blood product tracking log

Prehospital crews must undergo training for the proper care and storage of blood products. Products generally need to be kept between 1 and 6 °C. Crews must check products on a daily basis to ensure proper function of the storage refrigerator to maintain necessary temperatures, monitor expiration date, make sure products are free from contamination and proper functioning of transport coolers for missions. These responsibilities must be outlined in protocols for crews, as well as protocols for maintenance for the storage refrigerator and documentation of storage conditions. Policies must also be developed that outline how the blood will be transported on the vehicle or aircraft during missions.

Additionally, protocols must be adopted for ordering of new blood product units when transfused on a mission, as well as when products approach their expiration date. Agencies must work with their blood bank to determine when and how the products will be recycled back to an appropriate hospital blood bank for use in the general pool to prevent wastage. PRBC have a maximum shelf life of 42 days, liquid plasma of 21 days, and fresh frozen plasma of 5 days, although some lead time is necessary to allow for recycling into the blood bank inventory and release for transfusion prior to expiration. An inventory and expiration tracking log are essential and may be electronic or paper based.

Step-by-step protocols must be developed for the process and documentation of blood transfusion in the prehospital environment. The protocol must consider the applicable scope of practice to ensure transfusion falls within the scope of practice for the prehospital providers. Indications for transfusion must be clearly delineated, as well as process for direct medical command, and can be adapted from published protocols [73]. The protocol must also address monitoring, treatment, and documentation of potential transfusion reactions.

Finally, a strong quality assurance program is necessary. This must incorporate monitoring and benchmarking of appropriate patient selection for transfusion, transfusion reactions, product usage and recycling, as well as wastage due to expiration or out of range temperature. Thus, prehospital blood transfusion programs can come with significant expense in both equipment and training. An analysis of the thawed plasma air medical program employed in the PAMPer trial demonstrated an annual cost of $25,000–$30,000 per helicopter base; however, most of the cost was due to courier costs to recycle plasma units with a short shelf life of only 5 days [98]. They suggest that liquid plasma with a longer shelf life and efficient recycling systems can mitigate a significant proportion of this cost. Up-front costs can be an investment of well over $10,000, with maintenance costs of several thousand dollars annually; however, evidence suggests real benefits to patients, and we believe the costs are well worth it when feasible to implement.

Prehospital Resuscitation Adjuncts

Tranexamic Acid

Several resuscitation adjuncts have emerged as part of hemostatic and damage control resuscitation principles and are now receiving interest in the prehospital arena. The adjunct that has garnered the most attention is prehospital use of tranexamic acid (TXA). Since the CRASH-2 trial was published demonstrating a reduction in mortality from exsanguination when TXA was administered within 3 hours of injury and the greatest benefit when given within 1 hour of injury [99], prehospital administration has become an attractive therapeutic option. Subsequent military and civilian data suggested a potential increased risk of venous thromboembolic events despite potential benefits, highlighting the need for appropriate patient selection [100, 101] (see Chap. 11).

Several prehospital systems have implemented prehospital TXA protocols in both ground and air transport systems, showing early feasibility of TXA administration in the field [102, 103]. Given the recent implementation of TXA in the prehospital environment, long-term outcomes are lacking with mixed early results. A Swiss study demonstrated reduced fibrinolysis in 24 patients receiving prehospital TXA, but no change in clinical outcomes compared to a propensity-matched

cohort [104]. Neeki et al. propensity-matched 362 patients receiving prehospital TXA to a historical cohort and found lower mortality among patients receiving TXA, although there was no adjustment for secular trend and the study population had a low overall mortality rate [105]. Boudreau and colleagues found no difference in mortality for prehospital versus emergency department TXA administration; however, only 116 patients were included during the study period [106].

One criticism of the adoption of prehospital TXA based on the CRASH-2 trial is generalizability, as CRASH-2 was conducted in resource-poor environments without the capacity for damage control resuscitation. Thus, it's not clear the same benefits will translate to more developed trauma and prehospital systems that have the capacity to provide prehospital transfusion and early damage control resuscitation. To that end, there are three current multicenter randomized trials underway that evaluate prehospital TXA in developed trauma systems, including the STAAMP trial, the PATCH trial, and the Prehospital Tranexamic Acid Use for Traumatic Brain Injury trial (Table 29.1) [107]. The highly anticipated results of these trials will elucidate the efficacy and dosing of TXA in the prehospital environment.

Fibrinogen

Fibrinogen concentrate is another proposed adjunct for early resuscitation. Fibrinogen levels are the first to become critically low and are associated with higher mortality in both civilian and combat casualties with TIC [108–110]. Fibrinogen concentrate is logistically appealing for the prehospital environment as it does not require thawing or crossmatching, and high doses can be rapidly administered over minutes. Early results suggest potential mortality improvements in severely injured patients with TIC that received fibrinogen. Stinger et al. showed that higher fibrinogen in the form of plasma, cryoprecipitate, whole blood, or platelets per unit of PRBC in massively transfused patients was associated with reduced mortality [110]. Administration of fibrinogen concentrate based on thrombelastography led to lower than predicted mortality in one study [111]. Finally, universal administration of 3 g of fibrinogen concentrate led to higher survival compared to no fibrinogen or administration only when plasma fibrinogen levels were low among severely injured patients [112]. Prehospital data on fibrinogen administration, however, is lacking. Two ongoing trials are evaluating the effects of fibrinogen concentrate in prehospital resuscitation algorithms and will help to shed light on the potential benefits of this adjunct (Table 29.1) [45, 113].

Prothrombin Complex Concentrate

The final resuscitation adjunct that is receiving attention is prothrombin complex concentrate (PCC), available in either 3 factor or 4 factor formulations. PCC has gained popularity owing to its rapid reversal of vitamin K antagonist anticoagulation, particularly in patients with TBI [114]. PCC again is attractive for prehospital use given its ease of storage and administration. Evidence suggest that 4 factor PCC may reverse coagulopathy faster, resulting in fewer transfusions than 3 factor formulations [115]. A recent propensity-matched study demonstrated reduced mortality associated with coadministration of PCC with plasma compared to plasma alone in patients with TIC in the absence of vitamin K antagonist use [116]. An ongoing trial is comparing addition of PCC to fibrinogen concentrate for in-hospital resuscitation of patients with TIC [117]. Prehospital data on PCC is limited to case reports and 1 small case series of 34 patients receiving PCC for pre-injury warfarin anticoagulation from a rural air medical transport service demonstrating reduced time to reversal of anticoagulation [118–120]. PCC appears to show promise in the prehospital environment for patients with known vitamin K antagonist anticoagulation, particularly in the setting of TBI; however, this requires further study given the lack of robust data and potential for thrombotic adverse events in TIC patients without pre-injury anticoagulation.

Future of Prehospital Resuscitation

Whole Blood

Given significant benefits of PRBC and plasma administered in the field to injured patients, the future of prehospital resuscitation lies with optimizing prehospital transfusion strategies. Currently, the logistical challenges of storage and space restrictions limit widespread applicability. Prehospital transfusion programs are largely confined to air medical transport programs and a very small number of well-resourced ground transport agencies. The promising results of prehospital transfusion of both PRBC and plasma over a single blood product suggest the use of prehospital whole blood may be the ideal approach to prehospital resuscitation [55, 86]. Whole blood has long been used in the military, demonstrating improved survival over component therapy in combat casualties [121]. Recently, the Army Rangers have developed an O low-titer whole blood program to provide whole blood transfusion at the point of wounding.

Cold stored whole blood transfusion for trauma has gained increasing interest given the benefits of damage control resuscitation which aims to reconstitute whole blood through high component ratios. Initial safety of cold stored whole blood has been demonstrated [95]. Several trauma centers across the United States have added whole blood capabilities to their initial resuscitation algorithm of injured patients [92, 97, 122]. Whole blood is not without issues, however, including reduced and dysfunctional platelets. Future challenges involve improving platelet sparing filter technology for whole blood preparation.

Use of whole blood in the prehospital arena reduces the space required to carry and store both PRBC and plasma for prehospital agencies. Further, since PRBC and plasma have different shelf lives, using a single product (i.e., whole blood) reduces the risk for wastage and burden on prehospital providers to track and appropriately return PRBC and plasma on differing schedules.

Whole blood has begun to make its way into the prehospital environment in select locations. The Norwegian air medical transport program deployed cold stored whole blood in 2015 [92]. The Norwegian service has long had a progressive prehospital transfusion program given the challenging geography and long distances over 370 miles between trauma centers in the county. In Texas, two emergency medical service agencies near Houston became the first prehospital ground agencies to carry whole blood, followed shortly by air and ground providers in San Antonio [97, 123]. The Mayo Clinic transport program which has long been a proponent of remote damage control resuscitation has added cold stored whole blood to their capabilities recently [92]. These early implementors are collecting ongoing data to evaluate outcomes; however, no prospective comparative or randomized data exists for prehospital whole blood administration in trauma. Thus, investigators at the University of Pittsburgh are conducting a randomized pragmatic trial to evaluate the efficacy of prehospital whole blood compared to standard prehospital resuscitation practice with crystalloid and PRBC (Table 29.1) [46].

Freeze-Dried Products

Another exciting frontier for prehospital resuscitation is the use of lyophilized or freeze-dried products. The process involves applying low temperature, low moisture, and low pressure environment or spray-drying by aerosolizing the product into a high temperature chamber to remove moisture [124]. This obviates the need for cold storage of blood products in the prehospital environment. It also extends the shelf life to the order of years. Reconstitution is rapid and simple in the field with comparable physiologic activity [125], making freeze-dried products the ideal solution for prehospital resuscitation.

Lyophilization of red blood cells has been hampered by damage to the cells without cryoprotectants such as glycerol; however, significant progress has been made using novel processes

Fig. 29.5 RePlas® freeze-dried plasma kit manufactured by Teleflex® Incorporated. (Photo credit: Teleflex® Incorporated United States Securities and Exchange Commission Filing Form 8-K, May 3rd, 2018; available at: https://teleflexincorporated.gcs-web.com/node/18871/html)

that allow for small volumes of freeze-dried red blood cells with acceptable functional rehydration of cells [126]. Technology exists to freeze-dry platelets as well; however, the limiting factor has been safety concerns. Animal studies of lyophilized platelet transfusion demonstrate short activity, excess thrombogenicity, and splenic accumulation that limits clinical applicability in current form [127].

Freeze-dried plasma for prehospital use has been the focus of recent attention, particularly given the survival benefit seen in the PAMPer trial [39]. Freeze-dried plasma was used in World War II but abandoned due to high rates of hepatitis C (see Chap. 1), but pathogen reduction technology has eliminated this concern. Commercially available freeze-dried plasma products already exist from manufactures in Germany, France, and South Africa [128]; however, freeze-dried plasma is not Food and Drug Administration (FDA) approved for use in the United States due to historical concerns of infectious contamination risks [124]. Prehospital freeze-dried plasma has been used by French military and civilian trauma teams, Norwegian air medical transport services, and Israeli Defense Forces with data supporting feasibility in the prehospital environment [129–131]. A recent in-hospital pilot trial of freeze-dried plasma compared to fresh frozen plasma suggested freeze-dried plasma achieved higher fibrinogen concentrations and better thrombelastography parameters [132]. Large-scale studies of outcomes for prehospital administration of freeze-dried plasma are awaited from two ongoing phase III trials (Table 29.1) [133].

Freeze-dried plasma has received particular interest from the US military. The FDA recently approved the use of freeze-dried plasma for US military while evaluating civilian approval of the product [134]. The US Army is supporting the development of US-based freeze-dried products (Fig. 29.5) [133], and US special forces are currently carrying the French manufactured product [128]. The US military is also planning a multicenter trial to evaluate outcomes of prehospital freeze-dried plasma administration in collaboration with civilian trauma systems.

Summary

The onset of physiologic derangements including the development of TIC occurs within minutes of injury. Prehospital resuscitation is increasingly recognized to have significant influence on injured patients' outcomes. Intravenous access with large-bore peripheral sites is the standard, although intraosseous access is gaining popularity when patients are difficult to obtain intravenous access or are in extremis. Crystalloid is the

mostly widely available prehospital resuscitation fluid but has pro-inflammatory effects and can exacerbate TIC. Prehospital crystalloid volume should be minimized if any is infused, although patients with severe hypotension or TBI may benefit from a moderate amount of crystalloid when it is the only resuscitation fluid available. Prehospital blood product transfusion has shown improved outcomes over crystalloid and is rapidly becoming the standard of care for well-resourced air medical transport programs to treat hemorrhagic shock. Plasma in particular has strong supporting evidence in patients with prolonged transport times. Resuscitation adjuncts including tranexamic acid, fibrinogen concentrate, and prothrombin complex concentration are easily administered in the prehospital environment and show promise; however, prehospital outcome data are lacking. Whole blood may be an ideal resuscitation fluid in the prehospital setting, allowing damage control resuscitation in the field while minimizing the number of products that need to be stored, carried, and administered by prehospital providers. Logistical challenges of storage are the primary barrier limiting widespread prehospital transfusion programs, and freeze-dried products may eliminate these barriers, making prehospital damage control resuscitation accessible to all injured patients with hemorrhagic shock in the future.

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