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Is Fresh Frozen Plasma Still Necessary for Management of Acute Traumatic Coagulopathy?

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Abstract

Purpose of Review Massive blood loss secondary to major trauma is a leading cause of death worldwide. In recent years, multiple different strategies have evolved to counteract this life-threatening condition. In this review, we will review our understanding of trauma-induced coagulopathy and summarize current clinical transfusion regimes utilized in military and civilian settings. We will review currently available blood products used to rectify the coherent disturbances of haemostasis by outlining the characteristics of the different products.

Recent Findings Current evidence suggests that fresh frozen plasma and fibrinogen components play a fundamental role in trauma resuscitation with recent studies suggesting pre-hospital plasma and fibrinogen administration might also be beneficial in counteracting trauma-induced coagulopathy. Based on experience out of combat zones, whole blood transfusion might experience a renaissance in the future.

Summary Multiple different plasma-based products are available to treat and prevent trauma-induced coagulation disturbances. As randomized controlled trials in trauma population are difficult to conduct, most of the evidence is currently based on relatively small studies. While the overarching result of our review suggests the early use of plasma and fibrinogen products in combination with packed red blood cells will prevent trauma-induced coagulopathy, large, multi-centre studies are warranted to evaluate the long-term effects on patients' outcome.

Keywords Trauma · Coagulopathy · Fresh frozen plasma · Anaesthesia · Resuscitation

Introduction

Massive haemorrhage secondary to trauma is a leading cause of death worldwide necessitating blood component resuscitation. Military and civilian studies have shown an associated survival and morbidity benefit in trauma patients resuscitated with a high ratio of fresh frozen plasma (FFP) to packed red blood cell (PRBC) [1–5] and both European [6•] and North American [7] guidelines recommend an equal ratio of FFP to PRBC (and platelets). Some European authors have strongly recommended the initial use of factor concentrates for resuscitation in these casualties, although study results have not been conclusive [7, 8]. The presence of early hypofibrinogenemia in trauma patients is associated with an increased mortality [9], and the administration of fibrinogen concentrate (FC) has been shown to address this aspect of coagulopathy in trauma patients [10, 11]. Its use has subsequently gained favour in mainland European practice.

The initial acute traumatic coagulopathy (ATC) is a pathophysiological process that has been investigated extensively over the past two decades and is commonly described to include predominantly low fibrinogen and hyperfibrinolysis [12, 13]. The role of activated protein C (aPC) has been found to be a key element in this process [14], the activation of which lies at the site of the vascular endothelium [15] secondary to endothelial glycocalyx destruction [16]. FFP has been shown to have the ability to preserve the endothelial glycocalyx and consequently potentially improve survival. Despite

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evidence of the benefit of other components [17] and pharmacological adjuncts [18] in the resuscitation of bleeding trauma casualties, there is a strong argument that the continued use of FFP is a crucial element to a comprehensive resuscitation regime and remains a necessity in the management of coagulopathy in these patients.

Acute Traumatic Coagulopathy

The presence of reduced coagulation in trauma casualties or ATC has been known since before the Vietnam War [19]. One aspect of trauma-induced coagulopathy (TIC), defined by the "lethal triad" of hypothermia, acidosis and dilution, is understood to be potentially present later in a patient's pathway, and is generally understood to be a predominantly iatrogenic phenomenon, termed by some as resuscitation-associated coagulopathy [20] (Fig. 1). A separate pathological coagulation abnormality, ATC, has been identified that is found much earlier in the trauma process and temporally seems to be important on admission or in the pre-hospital environment.

In the last two decades, studies in Europe and the United States of America (USA) have found that some trauma casualties on admission to hospital are coagulopathic despite little or no haemodilution, no excessive acidosis and minimal reduction in temperature [21–23]. In civilian trauma casualties, the incidence of ATC is 24 to 34%, while in military ballistic casualties, ATC is present in up to 50% of patients [24–26] and is strongly correlated with mortality [27]. Other characteristics of ATC include low platelet counts, low clotting factors (factor V predominantly), low fibrinogen, fibrinolysis and reduced protein C levels [10, 28–30].

Activated Protein C

Hypovolaemia in casualties leads to tissue hypoperfusion and a hypoxic microcirculation, the main driver for ATC [31–33]. Tissue hypoperfusion produces a pathological amplification of protein C activation [34] which in turn has a negative feedback on thrombin production in addition to increasing fibrinolysis through removal of tissue plasminogen activator (tPA) inhibition [21, 34–38]. Increased injury severity and hypoperfusion increase the level of coagulopathy. An elevated level of APC is associated with an increased mortality [34, 39], and if inhibited experimentally in mice, coagulopathy is prevented [40].

Endothelial Glycocalyx

The endothelium has a vital role in the control and initiation of clotting. The surface of the endothelium is lined by a group of proteins linked with glycosaminoglycan chains termed the glycocalyx [41]. The glycocalyx, or rather its destruction, is an important intercessor for ATC development, and hypoperfusion is a crucial initiator of glycocalyx destruction. Syndecan-1 has been used in several studies as marker of glycocalyx destruction and damage. The glycocalyx has a key role in the pathophysiology of ATC with a number of theories linking the importance of the endothelium and coagulopathy. This is sometimes referred to as the "endotheliopathy of trauma" [42–44] or "shock-induced endotheliopathy" [45]. Trauma is not the only cause of endothelial pathology, however, with a number of factors being shown to produce evidence of glycocalyx disruption including hypoxia [46], sepsis [47] and traumatic sympathoadrenal activation [48]. Elements of all these are seen in hypo-perfused trauma patients so this response is not entirely unexpected.

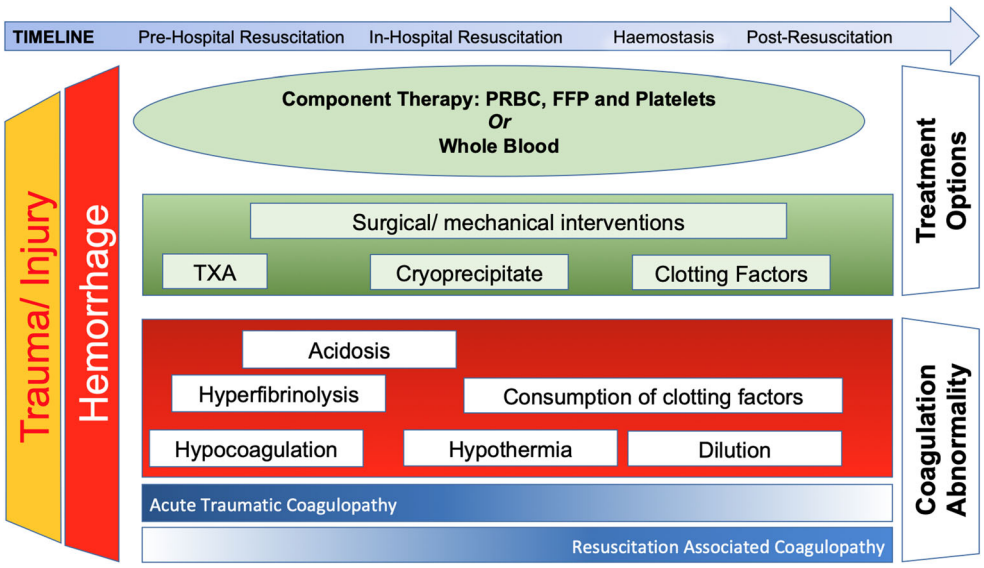

Fig. 1 Trauma-induced coagulopathies and treatment options

More recently, four different types of shock-induced endotheliopathy phenotypes have been identified with very different responses to trauma-induced endothelial damage [49••]. These data suggest an important role of individual genetic background in contributing to the endothelial response to trauma.

This review will elucidate our current understanding on trauma resuscitation regarding transfusion of plasma and plasma products (Fig. 1). We will also discuss the differences and advantages of component and whole blood transfusion regimes in trauma patients.

Component Therapy—Plasma and Other Therapeutics

Fresh Frozen Plasma

Fresh frozen plasma (FFP) is prepared from a single unit of whole blood or plasma collected by apheresis into a citrate-containing anticoagulant solution. It needs to be ABO compatible with AB being the universal donor type.

Once thawed, it requires transfusion within 4 h, or if that is to be delayed, it can be kept at 4 °C for up to 24 h; however, factor VIII (FVIII) activity will decline at 24 h by up to 28% [50]. Use can be extended up to 72 h with a decline in FVIII activity of 40%, although the activities of all other factors (including factors II (FII) and V (FV)) remain almost normal [51]. After 5 days, FVIII has lost 60% activity, FV 34% activity and the remainder less than 30% of activity [50, 52].

Risks of transfusion are similar to PRBC and include infectious disease transmission (ranging from 1:7.8 million for HIV to 1:153,000 for hepatitis B [53]), transfusion-associated cardiac overload, transfusion-related acute lung injury, acute haemolytic reactions and anaphylaxis [54–56].

FFP is a blood component that has been available since World War II [57]. It was initially used as a volume expander but is now primarily used in the management of haemorrhage and prevention of haemostatic abnormalities in bleeding and coagulopathic patients. The proof of its efficacy in the management of massive haemorrhage in a trauma casualty is disappointingly lacking [58]. Although it has been used to treat trauma haemorrhage for many years, there is surprisingly limited knowledge of its utility and application in this role. Inadequate transfusion is potentially associated with poor outcomes and undoubtedly blind over-transfusion can result in volume overload as well as additional donor exposure with increased rates of sepsis and multi-organ failure [59, 60].

Despite this lack of data, FFP has been widely recommended for use in major haemorrhage simultaneously with PRBC [1] at either specific doses of 10–15 mL/kg [61] or to achieve a lab coagulation level of no more than 1.5 times normal prothrombin time (PT) and activated partial thromboplastin time (aPTT) [62]. Other guidelines and recommendations counsel that it should be transfused in a specified ratio to PRBC. These vary according to continent as well as military or civilian use. However, some key guidelines from noteworthy international bodies do not specify a particular ratio. [63–67].

Lyophilised Plasma

Freeze-dried human plasma (FDP), otherwise known as lyophilised plasma (LP), was first introduced in World War II for use in resuscitation. Plasma was converted into a fine, lightweight powder in significant quantities to answer the high demand under difficult logistical. Disappointingly, there were high rates of viral disease transmission secondary to pooling of plasma units and inadequate screening so the concept was abandoned [68]. Modern screening methods have significantly reduced the risk of virus transmission and the concept of lyophilised plasma has re-emerged as a logistically superior alternative to FFP.

How does LP coagulation capacity compare to FFP? Investigations after World War II demonstrated its haemostatic function was similar as measured by PT [69]. In vitro assays of dried porcine plasma and FFP show similar coagulation profiles (FII, FVII and FIX, PT, aPTT and fibrinogen in addition to thromboelastographic assessments) [70, 71]. In vivo studies using swine models of polytrauma and haemorrhage demonstrate that FDP clotting factor levels are comparable with FFP with only a 14% drop in coagulation factor activity [70, 72]. Subsequent animal trauma models show LP is equally effective as FFP in reversing coagulopathy and improving physiological markers as well as survival [71]. In addition to coagulation benefits, Spoerke and colleagues [70] suggested LP might lower the inflammatory response as indicated by reduced IL-6 levels suggesting this secondary effect (to the use of ascorbic acid in its manufacturing process) was contributing to the advantage offered by LP during trauma resuscitation [73].

Although there is very little evidence of the efficacy of LP or FDP in humans, the military has been using LP and FDP justified by preclinical animal studies to meet the logistical demands of treating remote combat casualties. Currently, Dutch, French, Israeli, German and the United Kingdom (UK) armed forces use LP or FDP with US forces having just received FDA approval (personal communications).

The French military has the most experience and regularly advocate for LP based on its significant shelf life (2 years), speed of reconstitution (3 min to rehydrate), and similar clotting factor and fibrinogen activity compared with FFP [74, 75]. Two recently published studies by the French military report their experience at a Role 3 hospital in Kabul, Afghanistan: In the first study, they used LP in 87 military and civilian casualties and observed an overall mortality of 10% among patients receiving LP despite two-thirds of these patients being in haemorrhagic shock at treatment initiation

[76]. The second study looked at 72 transfusion episodes of which 63 received LP (average of 3 units) [77]. Like the first study, the authors noted a significant decrease in PT after LP administration. Though these studies are small and many patients were lost to follow-up, there were no reported complications attributable to LP administration.

Based on the combat data, several retrospective studies have examined the use of LP in the civilian pre-hospital environment. Data from Israel on 109 casualties over a 3-year period (83% penetrating, 50% multiple severe injuries) receiving FDP showed that it was both easy and feasible to use [78]. A French study demonstrated quicker delivery of blood products to trauma patients in a 1:1 ratio if LP is used instead of FFP [79] while a small dataset from Norway emphasizes the safety of use by pre-hospital helicopter emergency medical services (HEMS) [80].

The *Freeze-dried Plasma in the Initial Management of Coagulopathy in Trauma Patients* (*TrauCC*) *trial* was a prospective, randomized trial comparing the incidence of coagulopathy and fibrinogen levels in trauma patients receiving either French lyophilised plasma (FLyP) to FFP in a French hospital [81•]. The investigators found in the 48 patients enrolled that those in receipt of FLyP had higher fibrinogen concentrations and a more rapid improvement in their coagulopathy compared with FFP. Like previous studies, they also noted that FLyP patients received plasma quicker (15 min compared with more than 90 min) resulting in more rapid achievement of the target 1:1 FFP to PRBC ratio.

Despite the logistic advantages (i.e. lightweight, easily transportable, long shelf life), its limited availability and cost currently restrict ready access. These latter reasons are the principle rationalisation for its use only in austere situations in the British military—in the pre-hospital environment or with units who provide small surgical teams to areas that are more difficult to reach and support. Nevertheless, the small number of patients and the retrospective nature of most of these studies warrant future prospective randomized trials to evaluate clinical effectiveness and outcomes following LP transfusion.

Fibrinogen Concentrate

Fibrinogen depletion is considered a major challenge in trauma patients. Schlimp and colleagues found that patients with major trauma and an admission haemoglobin concentration lower than 100 g/L and base excess lower than − 6 commonly present with fibrinogen levels lower than 1.5 g/L [82]. Similarly, Rourke and colleagues found low fibrinogen levels in 41% of the patients with hypotension on admission, increased shock severity and high degree of injury (injury severity score, ISS ≥ 25) [10]. Specific fibrinogen replacement is arguably a key factor in trauma casualty resuscitation.

Fibrinogen concentrate (FC) is produced from pooled human plasma and stored as a lyophilised powder at room temperature [83]. It can be reconstituted rapidly with sterile water for immediate administration [84]. Viral infection risk is minimal as viral inactivation by exposure to solvent or pasteurisation occurs in the manufacturing process [85]. Unlike cryoprecipitate, the concentration of fibrinogen is standardized and there is no requirement for cross matching [84]. One study showed that 2 g of FC would increase plasma fibrinogen by 0.44 g/L, compared with only 0.26 g/L after 10 units of cryoprecipitate infusion (~ 1.8–2.2 g of fibrinogen), suggesting a superiority over cryoprecipitate; some have even reported a reduction of fibrinogen after infusion of cryoprecipitate [86].

Fibrinogen supplementation in cases of severe bleeding demonstrate an improvement in coagulation parameters [87–89], increased plasma fibrinogen levels and survival [87, 88, 90], and reduced transfusion requirements [88, 89]. However, a recent meta-analysis found no improvement of mortality in trauma patients by administration of FC, although recognizing the poor quality of included studies [91].

Subsequent trials aimed to overcome this limitation: In the *Fibrinogen in the Initial Resuscitation of Severe Trauma* (*FiiRST*) *trial*, FC was given within an hour of hospital arrival [92]. Despite fibrinogen levels being higher (up to 12 h), mortality did not differ between the groups. This may have been due to a lack of difference in transfused blood products with both groups receiving similar amounts of cryoprecipitate. The *Reversal of Trauma Induced Coagulopathy Using Coagulation Factor Concentrates or Fresh Frozen Plasma* (*RETIC) trial* [8] investigated the use of FFP versus coagulation factor concentrates. They used fibrinogen concentrate predominantly but the trial was abandoned due to the need for significant rescue therapy in the FFP group. Just over half of the FFP group needed rescue compared with 4% receiving FC with the number needing massive transfusion also greater in the FFP group (30% vs. 12%). Despite this study being stopped early, their findings suggest that FC should be looked at in a favourable light.

One more recent trial undertook a retrospective look at giving FC pre-emptively in trauma patients with higher ISS rather than waiting for threshold results [93]. Nearly 60% of the patients with an ISS of greater than 26 received 10 units of PRBC and found to have low serum fibrinogen. The 48-h mortality rate of those with ISS greater than 26 was 8.6% in the pre-emptive FC group compared with 22.9% in the standard treatment group. When ranking patients according to the ISS, the authors found that pre-emptive administration reduced mortality from 50 to 20% in patients with an ISS of greater than 41.

Similar results were presented by Itagaki and colleagues [94] in a recent study. Although limited by its retrospective nature, this study illustrates a mortality benefit when FC is given early and most definitely leads to the question of whether it should be taken into the pre-hospital environment (both civilian and military).

Prothrombin Complex Concentrate

Prothrombin complex concentrates (PCC) are intermediate purity pooled plasma products containing a mixture of vitamin K-dependent coagulation factors [95, 96] produced by ion-exchange chromatography of either three- (II, IX and X) or four-factors (addition of VII). The concentration of coagulation factors results in a 25 times higher clotting potential than normal plasma [97]. Although developed for the treatment of haemophilia B, PCC are now frequently used to treat congenital and acquired deficiency of vitamin K-dependent clotting factors [95].

The use of PCC in the treatment of trauma casualties has gained popularity in Europe with several studies comparing it with FFP in casualty resuscitation. In a porcine trauma model, the use of PCC leads to reduced time to haemostasis and number of blood products transfused [98]. Translational human studies have had similar findings with the use of PCC reducing time to correction of coagulopathy [99], reduced blood use [99] and reduced mortality. Unfortunately, the majority of these studies compare PCC and FFP with FFP alone rather than PCC alone [99, 100]. There remains no evidence of mortality benefit with PCC use. The reported morbidity benefit of normalization of haemostasis was measured in conventional laboratory coagulation measures and remained prolonged in all groups, although a difference between them was evident.

Whole Blood Transfusion

Although used by the military since World War I [101], both stored and fresh whole blood (FWB) are seeing increased usage in some trauma settings because these products may be logistically easier and less wasteful compared with classical multi-component transfusion strategies. Thereby, low-titre group O whole blood (LTOWB) has to be distinguished from leukoreduced, and leukoreduced whole blood using a platelet-sparing filter products provided by the American Red Cross (ARC) [102, 103]. Evaluated in regard to clotting factor activity in the presence of PRBCs, Huish and colleagues demonstrated that the factor activity remained above 50% despite prolonged storage (i.e. up to 35 days) and the presence of platelets [104]. Leukoreduced blood transfusions have become standard in most trauma centres, and therefore, transfusion of LTOWB through leukoreduction filters have been evaluated in regard to its haemostatic properties. Importantly, despite the fact that platelet count decreased during cold storage, haemostasis as assessed by thrombelastography and PFA-100 tests was not diminished over a 2-week storage period [102]. Praised by the military [105], whole blood products remain to be evaluated for its suitability during civilian trauma resuscitation.

Resuscitation in Trauma

The arguably pivotal study and a critical report for military resuscitation was from Borgman et al. based in Iraq [1] who looked at massive transfusions in 246 military combatants. All casualties had received more than 10 units of components in 24 h with FFP to PRBC ratios divided into 1:8, 1:2.5, and 1:1.4, respectively. The highest ratio resulted in both a 55% absolute reduction in mortality and increased survival time compared with the lowest FFP to PRBC ratio. Despite these dramatic results, concern about survivor bias tempered these findings and has led to further work.

The most recognized study investigating blood compound therapy is the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial [5], studying 680 trauma casualties suffering (or suspected to be suffering) from massive haemorrhage. The authors compared transfusion of FFP, platelets and PRBC in a 1:1:1 ratio compared with a 1:1:2 ratio. Although no long-term survival benefits were found between the two groups, the 1:1:1 group achieved haemostasis and had fewer deaths due to exsanguination at the 24-h mark. It should be noted that deaths primarily due to haemorrhage most commonly occur in the first 24 h. After 24 h, the proportion dying due to other causes—multi-organ failure, head injury and others—becomes more prevalent.

A number of the authors have investigated civilian trauma in their home trauma centres on return from their military deployment [3]. They found a similar survival advantage in the high ratio group, but a markedly dissimilar time to death (35 h compared with 4 h). Although the work by Borgman et al. was used as support for the fixed ratio resuscitation of military ballistic casualties, the authors disclosed that there was a survivorship bias. The patients, who died early, did so before they were able to get more FFP, and hence, their ratios were high. In contrast, a patient with less shock and less physiologically challenged by their injuries survived long enough to get more FFP, and as a result of having lesser injuries, their FFP to PRBC ratio was higher [106], suggesting injury severity was the cause of mortality difference, not the specific ratio of transfused blood products.

Interestingly, while initial studies suggested that prolonged storage time of PRBC may negatively impact patients outcome [107], more recent data suggested that storage time does not impact patients' outcome in severely injured patients [108, 109]. In summary, a wide range of both military and civilian retrospective studies on early empirical ratio haemostatic resuscitation are available [2, 110–120], with the majority suggesting that higher ratios of FFP to PRBC will significantly reduce the mortality of bleeding trauma casualties. These mortality reductions ranged from 15 to 62% and originated mainly from civilian trauma centres in the USA and Europe.

PRO Plasma—Resuscitation with Plasma Products

As the glycocalyx is particularly sensitive to injury during ATC, the administration of FFP has been proved to be beneficial for its function. A prospective, observational study in severely injured patients with haemorrhagic shock demonstrated that resuscitation with FFP resulted in a 3-fold decrease of circulating syndecan-1 [121]. Although the levels were higher than normal healthy patients, this significant decrease illustrates the potential of FFP to protect and even restore the glycocalyx.

Plasma-based resuscitation of trauma patients in haemorrhagic shock certainly reduces mortality [1, 3, 120]. Recently, these data have been extended to the preclinical application of FFP. The *Prehospital Air Medical Plasma* (*PAMPer*) trial demonstrated that patients receiving FFP-only resuscitation in the pre-hospital environment had a significantly lower mortality with minimal adverse effects compared with conventional resuscitation regimes [122, 123]. By administering 2 units of FFP before any resuscitation fluid, 30-day mortality decreased by 10%. Importantly, transfusion of FFP did not delay the transport time to the trauma centre (42 vs. 40 min).

A paucity of evidence of the detrimental effect of plasma in conjunction with good evidence that it is beneficial for treating the pathophysiological origin of ATC intimates that FFP is crucial in managing and resuscitating trauma casualties with ATC. Considering the impaired coagulation cascade, FFP and plasma products constitute one of the main components of a multiple-component transfusion strategy.

CONTRA Plasma—Whole Blood Transfusion or NO Plasma

In a recent review, Spinella suggested that transfusion of FWB in haemorrhage may result in favourable outcome [17] according to recent studies on combat casualties in Iraq [124] and Afghanistan [125]. The advantage of refrigerated storage for stored FWB compared with multiple storage options for components, including agitation requirements for stand-alone platelets, means FWB has a significant logistical advantage [126]. Concerns over infection and grouping mismatch are valid, with 2 infections and one transfusion-associated graft versus host fatality in 10,000 FWB transfusions on US personnel [127]. Nevertheless, FWB has been more frequently used with at least 5 trauma centres in the USA and Norway studying LTOWB for trauma resuscitation [128]. Simultaneously, a number of larger studies (*LITES Network, NCT03402035*) are beginning to investigate the feasibility and potential advantages of LTOWB in trauma resuscitation (Table 1).

The UK military experience so far has been sporadic and has centred on emergency donor panel provision in response to patient extremis or when platelet provision was inadequate or non-existent. FWB has considerable potential, particularly in the pre-hospital environment and in austere military environments. Unfortunately, within the UK at present, National Health Service (NHS) Blood and Transplant does not supply FWB as standard. Despite this, requests from the UK military and other agencies have had recent impact, and the London helicopter emergency medical service are currently undertaking a study on its use for pre-hospital trauma resuscitation (*RABBIT trial, NCT03522636*).

A recent survey by the ARC demonstrated an increased acceptance of FWB transfusion in trauma patients [129••]. Although 80% of responding trauma centres reported using component therapy without laboratory guidance for the management of massive blood transfusion, 10% of the respondents mainly from hospitals of less than 550 beds confirmed using FWB as part of their transfusion regime [129••]. Furthermore, most responders preferred low-titre WB over leukoreduced FWB using platelet-sparing filters.

As the fibrinolysis and lack of fibrinogen appear to be major features of ATC [31], balancing these deficits by fibrinogen replacement appears clearly beneficial for mortality [10, 93]. This strategy would not be sufficient alone since successful resuscitation requires replacement of volume and therefore alternatives to excessive crystalloid [130] or colloid solutions [131] might only be available through transfusion of FWB or single components.

Table 1 Advances and disadvantages of different transfusion regimens in acute traumatic resuscitation

	Plasma-based component therapy	Whole blood transfusion
Pro	• Individualized • Available in many hospitals • More easily achievable in pre-hospital/austere environments with caveats • Corporate memory • Designed to prolong storage time	• Easy transfusable • All aspects of fluid resuscitation included
Contra	• High maintenance costs • Does not reflect natural component ratios • Some uncertainty of best ratio to use • Usual time delay to get platelets and cryoprecipitate	• Short storage time • Decrease in some clotting factors over time • Not widely established yet • Probable higher infection risk • Majority of clinicians have not used • Potential greater wastage

Therefore, the first report of using FWB for civilian trauma resuscitation might be considered as guidance for future patient care in this particular setting [132].

Conclusion

A number of potential alternatives to plasma have been investigated but none have yet proven to be a realistic option. PCC and FC have proven benefits and are key additions in trauma resuscitation of patients with ATC. FWB is probably one of the more realistic alternatives; however, the universal lack of availability and clinical evidence limits its current use despite the excitement of some institutions (i.e. ARC. For the time being, plasma resuscitation at ratios approaching 1:1:1 with PRBC and platelets appears to be the most appropriate resuscitation regime in treatment of ATC (Table 1).

Abbreviations aPC, Activated protein C; aPTT, Activated partial thromboplastin time; ARC, American Red Cross; ATC, Acute traumatic coagulopathy; FC, Fibrinogen concentrate; FDA, US Food and Drug Administration; FDP, Freeze-dried human plasma; FFP, Fresh frozen plasma; FLyP, French lyophilised plasma; FVIII, Coagulation factor VIII; FWB, Fresh whole blood; ISS, Injury severity score; LP, Lyophilised plasma; LTOWB, Low-titre group O whole blood; PCC, Prothrombin complex concentrate; PRBC, Packed red blood cell; PT, Prothrombin time; PT, prothrombin time; tPA, Tissue plasminogen activator

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- •• Of major importance

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