Four-factor Prothrombin Complex Concentrate Use for Bleeding Management in Adult Trauma

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Trauma remains a leading cause of death in adults, despite advancements in emergency medical care.[1] Despite advances in understanding the underlying pathophysiology, leading to reductions in mortality rates, up to 35% of severe trauma patients still present with coagulopathy upon hospital admission.[2] Exsanguination remains a leading cause of death in these patients, accounting for up to 14.6% of fatalities due to severe bleeding.[3] Bleeding and hemorrhagic shock contribute to trauma-induced coagulopathy (TIC), influenced by factors including the nature of the injury and the type of resuscitation.[4]

Hemostasis is based on the potential of the blood to produce thrombin (thrombin generation) and the downstream effects of thrombin on coagulation, anticoagulation, fibrinolysis, and the vascular endothelium.[5] According to the cell-based concept of coagulation, hemostasis begins with the initiation phase, which is characterized by the involvement of tissue factors and phospholipids and leads to the initial production of small amounts of thrombin. The production of thrombin activates platelets, factor V, and factor VIII and leads to the second phase (propagation phase) of coagulation. In this phase, thrombin production increases rapidly and forms a hemostatic plug. Hemostasis concludes with the termination phase, in which various inhibitory mechanisms regulate the amount and duration of thrombin production and prevent excessive clot formation. Conventional coagulation tests such as prothrombin time (PT) have been used to identify patients at risk of TIC (and associated mortality[6]) and to measure (vitamin K–dependent) clotting factor levels. However, these tests are inadequate for assessing the overall response of the hemostatic system because they cannot measure circulating clot initiators or inhibitors involved in the termination phase. To overcome this limitation, thrombin generation assays have been developed to assess components of all three phases of hemostasis.[7] *In vivo*, thrombin generation potential can be assessed by measuring the thrombin–antithrombin complex and prothrombin fragments 1 + 2 (F1 + 2), whereas *in vitro* thrombin generation assays assess the endogenous capacity of the total hemostatic potential.[8] The *in vivo* and *in vitro* assays are therefore not identical and must be used and interpreted in a differentiated manner. Thrombin generation is most sensitive to prothrombin levels (increased thrombin generation) and antithrombin levels (decreased thrombin generation) but can also be perturbed by hemodilution, coagulation factor consumption, shock-induced systemic acidosis, and hypothermia.[9]

Patients with severe trauma and coagulopathy often present with reduced levels of factors V, VII, and X and fibrinogen early after injury.[10–13] Data on reduced activity of coagulation factors after severe injury are inconsistent. Further, decreased concentrations of procoagulant factors are not necessarily associated with a lower rate of thrombin generation expressed in some analyses. Trauma patients can present with decreased procoagulants but increased

Peter Nagele, M.D., M.Sc., served as Handling Editor for this article.

Submitted for publication July 6, 2024. Accepted for publication September 11, 2024.

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 Anesthesiology 2024; XXX:XX–XX. DOI: 10.1097/ALN.0000000000005230

The article processing charge was funded by the University of Bern, Bern, Switzerland.

<zdoi;10.1097/ALN.0000000000005230>

thrombin generation biomarkers compared to those without injury or TIC. In addition, certain procoagulant microparticles can enhance thrombin generation, despite a lack of procoagulant factors.[7] In trauma patients, peak thrombin generation was higher than in healthy individuals, despite prolonged standard coagulation tests. Trauma patients exhibit 2.5-fold higher average plasma thrombin generation capacity on hospital admission than uninjured individuals.[14] However, 17% of severely injured patients showed low thrombin generation capacity and peak concentration, leading to a fourfold increase in 30-day mortality.[14] Hemostatic resuscitation approaches to restoring thrombin generation in trauma vary with massive bleeding and focus on fresh frozen plasma (FFP) to replace soluble coagulation factor deficiency and restore hemostasis. However, *in vitro* and clinical studies suggest inefficient thrombin generation recovery after FFP transfusion alone.[15,16] Holcomb *et al.*[3] reported on a large randomized clinical trial in which hemorrhagic traumatic shock resuscitation was driven by fixed ratios of blood products. Although this method has been widely shown to be effective, no significant differences in morbidity or mortality were observed with higher FFP ratios in cases of severe trauma and major bleeding. Conversely, first-line treatment with four-factor prothrombin complex concentrate (4F-PCC), as part of a coagulation factor concentrate-based hemostatic approach guided by viscoelastic point-of-care (POC) coagulation monitoring to reversing TIC, rapidly restores clot strength and reduces the need for allogeneic blood products. However, it is important to note that this evidence is derived from a small clinical trial and carries certain limitations.[17] One advantage of 4F-PCC over FFP is its ability to deliver high doses of vitamin K–dependent clotting factors to restore hemostasis more effectively and faster. The availability of a resource that can be rapidly and easily administered in austere environments with limited access, especially when prolonged transfers to medical centers are expected, would be highly valuable and appreciated. The 4F-PCC compound undergoes a viral pathogen inactivation process during manufacturing, which enhances its biologic safety. Additionally, some formulations can be stored at room temperature, are easily reconstituted, and can be administered intravenously, making them particularly advantageous in emergency situations in which rapid resolution of trauma-induced coagulopathy is critical. However, the efficacy and safety of 4F-PCC in treating TIC remain uncertain, without consensus on indications, timing, adjunct transfusion therapies, and dosage regimens.[18] In addition, in a study examining commercially available PCC, notable differences were found in their composition and functional activity, despite being standardized based on FIX antigen levels. The research revealed variations in protein content, the presence of additives such as heparin and antithrombin, and the ability to generate thrombin. These differences, influenced by heparin, antithrombin, and other proteins, affect the hemostatic properties of the PCCs, potentially affecting clinical outcomes and the risk of thromboembolism. The study highlights the importance of treating each PCC as a distinct agent, with individualized safety and efficacy profiles, and advises caution when substituting products. These data are crucial for selecting PCCs, especially when neutralizing new oral anticoagulants.[19]

This review explores studies on the use of 4F-PCC for trauma-related bleeding in adults, focusing on its indications, monitoring, and management strategies aimed at optimizing patient outcomes. Although plasma's undeniable benefits, such as blood volume expansion, glycocalyx protection,[20] and replacement of coagulation factors, are acknowledged, a detailed comparative evaluation of plasma *versus* 4F-PCC in the management of traumatic hemorrhagic shock is beyond the scope of this discussion.

Pharmacology of Four-factor Prothrombin Complex Concentrate

The coagulation activity (measured in IU/ml) of lyophilized 4F-PCC is based on factor IX content, although the concentrations of other factors vary between products, as well as other anticoagulant proteins such as protein C, protein S, and variable amounts of heparin (0.2 to 0.5 IU per IU of factor IX), antithrombin III, and human albumin, which are not therapeutic. This gives the various products on the market a certain specificity in terms of their activity, without any major differences in their efficacy.[21] Three-factor prothrombin complex concentrate (3F-PCC; *e.g.*, Profilnine SD, Grifols Biologicals Inc., USA) contains factors II, IX, and X and a relatively low concentration of factor VII (less than or equal to 175 IU per 500 IU PCC). In contrast, 4F-PCC (in Europe: *e.g.*, Beriplex, CSL Behring; Octaplex, Octapharma; in the United States: Kcentra, CSL Behring, approved by the Food and Drug Administration for the urgent reversal of anticoagulation by vitamin K antagonist therapy in adult patients with acute major bleeding or need for urgent surgery/invasive procedures), includes a high concentration of factor VII (180 to 500 IU per 500 IU PCC),[21] affecting the extrinsic, tissue-factor induced coagulation pathway. 4F-PCC also contains antithrombotic proteins C and S, small amounts of heparin (0.2 to 0.5 IU per IU factor IX), antithrombin III, and human albumin.[21–24] Modern 4F-PCC is the primary treatment option for the emergent reversal of coagulopathy associated with vitamin K antagonists (VKAs).[21,25,26] In healthy individuals, factor II (prothrombin) exhibits an elimination half-life of 60 h. The other procoagulant factors have a half-life of approximately 40 h, whereas the antithrombotic proteins are eliminated in greater than 50 h.[22] A recent review of post-marketing pharmacovigilance safety report analyses showed that treatment with 4F-PCC across multiple indications was associated with few adverse reactions and a low rate of thrombotic events, confirming a positive safety profile for 4F-PCC.[27] However, rapid administration of 4F-PCC, combined with the prolonged half-life of prothrombin and

the imbalance of pro- and anticoagulant proteins, raised concerns about thromboembolic complications. Risk factors for thrombosis should be considered to increase the safety of 4F-PCC.[28] Indeed, massive acute thromboembolism shortly after 3F- and 4F-PCC administration has been reported.[29,30] In a preclinical safety study with 15 healthy volunteers, the infusion of 50 IU/kg of 4F-PCC did not result in clinical evidence of thrombosis. Transient elevation of the thrombogenic markers F1 and 2 was observed 15 min postinfusion, subsiding after 3 h and returning to baseline by 24 h, with no changes in plasma D-dimer concentrations.[22] Although 4F-PCC has been used in Europe for decades, safety data from prospective randomized clinical studies are limited to two recent larger studies from the same group from the United States, comparing 4F-PCC *versus* FFP for urgent VKA reversal.[31,32] An integrated safety analysis from these studies showed thromboembolic events in 7.3% of the 4F-PCC group and 7.1% of the FFP group.[33,34] The observational REVERSAL study analyzed data from two large healthcare systems in Southern California from 2008 to 2020.[35] In the 1,119 patients who received 4F-PCC for the urgent reversal of VKA therapy, matched 1:1 to those treated with FFP, the 45-day risk of thromboembolic events was 3.4% *versus* 4.1% in the FFP group (adjusted hazard ratio, 0.76; 95% CI, 0.49 to 1.16; $P = 0.25$).[35] In a porcine model of coagulopathy with liver injury treated with 50 IU/kg PCC, 44% of the animals developed disseminated intravascular coagulation and other thromboembolic complications, especially when 4F-PCC was coadministered with fibrinogen concentrate.[36] Adding antithrombin III seemed to reduce this risk.[37] In another animal model comparing the thrombogenic potential of 4F-PCC, activated PCC, and recombinant activated factor VII, 4F-PCC was found to have the lowest risk, making it more suitable for reversing coagulopathy in bleeding patients.[38]

Monitoring of Four-factor Prothrombin Complex Concentrate Effects

Effective monitoring of 4F-PCC therapy is essential to maximize its benefits and minimize potential risk, such as thromboembolic events. Conventional coagulation tests, such as PT and international normalized ratio (INR), are partially useful for detecting coagulation factor deficiencies. Although INR is standardized for monitoring VKA therapy and can guide 4F-PCC administration, PT is a test that may not provide immediate results. Moreover, both PT and INR can be influenced by various factors and may not fully reflect the complexities of TIC or the rapid fluctuations in plasma coagulation factor levels after 4F-PCC administration.[39] However, when measured with certain point-of-care devices, these tests have proven to be useful.[40] Thrombin generation assays, using the calibrated automated thrombogram method, could offer a suitable alternative, although it does not provide a quick result either, and it is not widely available for clinical use, nor for guiding and monitoring 4F-PCC therapy.[41] Thrombin generation assays have been investigated in patients whose anticoagulation has been reversed due to bleeding, including those treated with VKAs or factor Xa inhibitors. In VKA-treated patients, thrombin generation assay parameters returned to normal values post–4F-PCC administration, whereas in factor Xa inhibitor–treated patients, thrombin generation assay parameters remained above the normal range after receiving a mean dose of 49 IU/kg of 4F-PCC.[42] Although these results are promising and might support thrombin generation assay use in bleeding patients, thrombin generation assays require platelet-poor plasma and meticulous execution, which limit their routine use in emergency settings where precision is crucial and time is of the essence. To date, none of the thrombin generation assays have been applied in bleeding trauma patients, and therefore, they cannot be considered routine in this setting.[43]

Coagulation therapy in clinical trauma settings is primarily guided by conventional coagulation assays or viscoelastic POC assays, as potential surrogate markers of thrombin generation.[44–47] In the Early Administration of Prothrombin Concentrate Complex in Patients With Acute Hemorrhage Following Severe Trauma (PROCOAG) multisite randomized clinical trial, the PT ratio (prothrombin time/laboratory normal reference value) was used to delineate trauma-related coagulation factor deficiency. Acute traumatic coagulopathy was defined by a PT ratio greater than 1.2, whereas severe acute traumatic coagulopathy was characterized by a PT ratio exceeding 1.5.[48] A systematic review and meta-analysis of 23 mostly observational studies indicated that a dose of 20 to 30 IU/kg of 4F-PCC for TIC was typically initiated when coagulation analysis showed an INR of greater than or equal to 1.5 or a clotting time (CT) longer than 80 s in the extrinsically activated thromboelastometry (EXTEM) assay after administering fibrinogen concentrate. This approach did not significantly reduce mortality or increase venous thromboembolism.[24] Current practices in large European trauma centers and European recommendations (*e.g.*, European Trauma Guidelines)[47] for managing trauma patients with major bleeding favor a coagulation factor concentrate-based management strategy.[49,50] European guidelines state that after administering sufficient amounts of fibrinogen concentrate to achieve a fibrinogen level greater than 1.5 g/l, the EXTEM CT should be normalized using 4F-PCC if it remains prolonged. Data from two prospective studies in warfarin-treated individuals showed a strong correlation between reduced thrombin generation, INR, and CT prolongation in the EXTEM assay.[51,52] These findings imply that EXTEM CT is more sensitive to coagulation factors II, X, and VII deficiencies than assays activated *via* the intrinsic contact pathway. Therefore, EXTEM CT could serve as a monitoring tool for 4F-PCC in trauma cases with deficiency in extrinsic pathway coagulation factors. Figure 1 provides a visual summary of a clinical monitoring and management approach for 4F-PCC based on surrogate markers of thrombin generation.

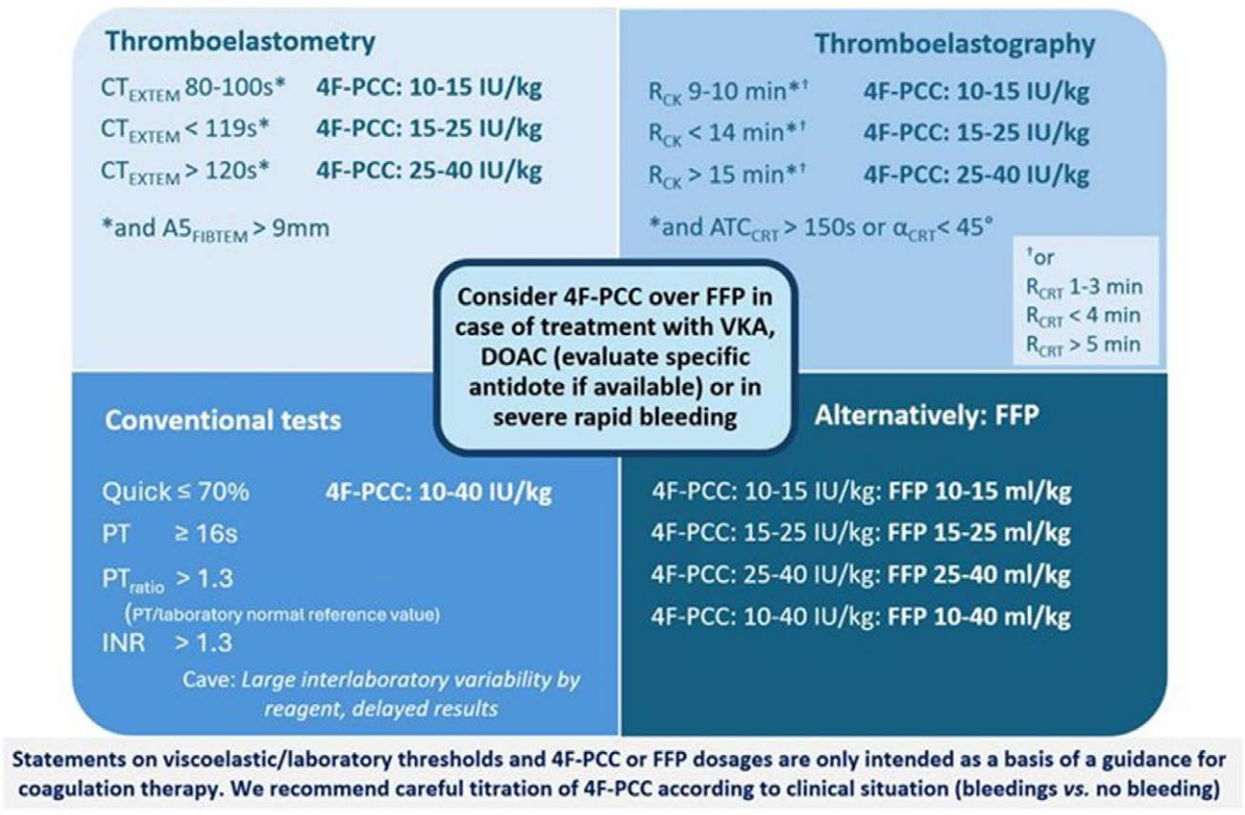

Fig. 1. Clinical monitoring and management approach for four-factor prothrombin complex concentrate (4F-PCC) as an option for trauma bleeding resuscitation strategy. ACT, activated clotting time (in seconds); α, alpha angle; A5, amplitude at 5 min after CT (in mm); CT, clotting time, in seconds; CK, citrated kaolin test; CRT, citrated rapid TEG test; DOAC, direct oral anticoagulants; EXTEM, extrinsically activated thromboelastometry assay; FIBTEM, fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D; FFP, fresh frozen plasma; INR, international normalized ratio; IU, international unit; PT, prothrombin time; R, reaction time (in min), VKA, vitamin K antagonist.

Clinical Evidence for Prothrombin Complex Concentrate in Trauma

Evidence specifically supporting the clinical use of 4F-PCC for trauma-related bleeding is currently lacking, because systematic reviews often fail to differentiate between the effects of 3F- and 4F-PCC compounds. Additionally, due to the limited availability of 3F-PCC, obtaining robust data for this compound in the future seems unlikely.[24,53–55] The main trauma-related pathophysiologic conditions that might benefit from 4F-PCC are summarized in figure 2. The use of 4F-PCC for trauma-related bleeding, aside from VKA reversal, is considered off-label in the United States. However, in Europe, it is an on-label treatment when trauma-induced coagulopathy is accompanied by impaired thrombin generation.[21,47]

Prothrombin Complex Concentrate for Anticoagulant Reversal

4F-PCC is well established for its on-label use in emergency reversal of VKA,[21,25,26] and studies consistently show that it is more effective than FFP. As a result, it is widely recognized as a validated and highly effective therapeutic option.[31,32,56,57] The noninferiority of fixed-dose *versus* tailored-dose 4F-PCC has not been definitively demonstrated,[58] with some studies indicating effectiveness and safety for both.[59–61] Despite the pharmacologic differences and the heterogeneity in study designs and outcomes, meta-analyses comparing 3F- and 4F-PCC have generally concluded that 4F-PCC is more effective in achieving target INR levels, with a similar safety profile.[23] 4F-PCC has also been investigated for the reversal of direct oral anticoagulants (DOACs) in cases of DOAC-related bleeding and nonbleeding situations. In this entity, it is considered a possible aid to counteract, if not completely reverse, its effect.[25,62–68] Low-dose 4F-PCC (25 IU/kg) has been proposed as a cost-effective alternative to high-dose 4F-PCC (50 IU/kg) for the acute reversal of factor Xa inhibitors, providing effective hemostasis without increasing the risk of thromboembolic events or in-hospital mortality.[63] A recent qualitative review suggests that both low and high doses of 4F-PCC may offer similar clinical effectiveness

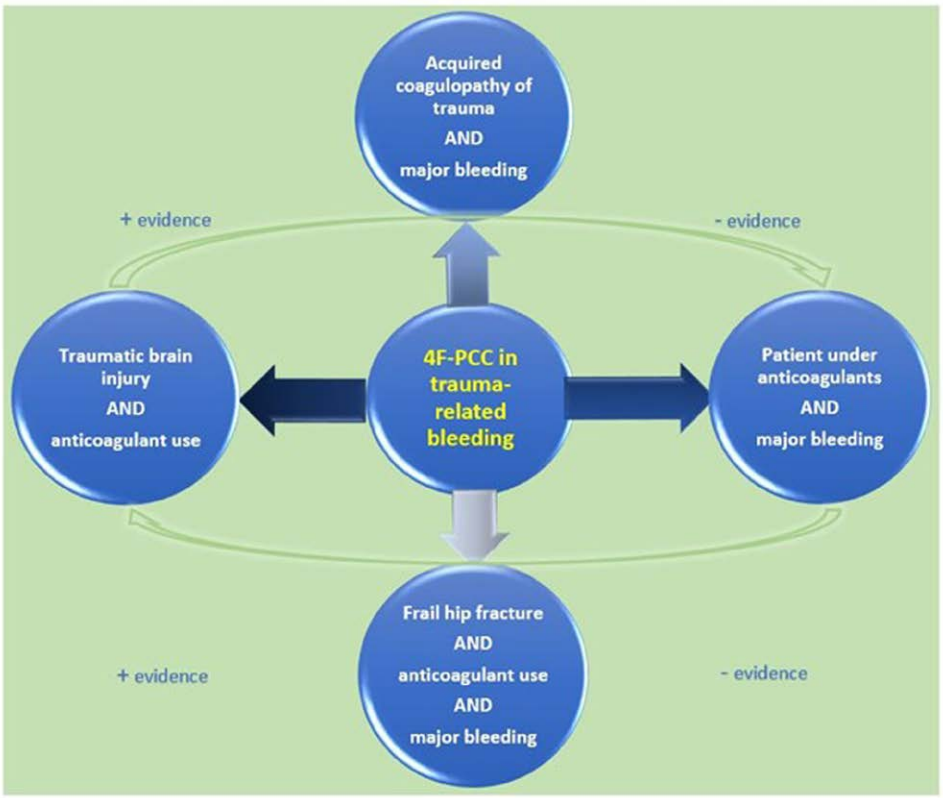

Fig. 2. Key trauma-related pathophysiologic conditions that may benefit from four-factor prothrombin complex concentrate (4F-PCC). +, good evidence available; –, less evidence available.

and safety.[68] Meta-analyses have compared andexanet alfa with PCC for urgent reversal of anti-factor Xa–associated bleeding.[64,65] Although there are concerns about comparing the different types of PCC (3F, 4F, and activated) due to their pharmacologic differences and lack of uniformity, the included studies do not show significant differences in efficacy or thromboembolic risk profiles between PCC and andexanet alfa. Observational data, however, suggest that andexanet alfa may be associated with lower in-hospital and 30-day mortality compared to 4F-PCC.[66] An *in vitro* study on thrombin generation indicated that 4F-PCC normalized values in the presence of low or narrow range factor Xa inhibitor concentrations (less than 75 ng/ml).[67] A recent experimental study in healthy adults evaluated the *ex vivo* reversal capacity of andexanet alfa, 4F-PCC, and activated PCC in rivaroxaban-anticoagulated blood at different plasma concentrations using conventional coagulation assays, thrombin generation assay, and viscoelastic tests. This study concluded that high-dose 4F-PCC showed similar efficacy to andexanet alfa when simulating *in vivo* thrombogenicity potential under arterial flow conditions.[69] In experimental settings, both idarucizumab and PCC have demonstrated effectiveness in reversing traumatic bleeding associated with dabigatran, with idarucizumab being preferred for urgent reversal. However, 4F-PCC may be valuable when the anticoagulant is unknown or idarucizumab is unavailable. Studies have observed benefits from combining minimum doses of different reversal agents.[70] The use of activated PCC is neither widespread nor recommended for the trauma patient with bleeding,[38] and a few nonrandomized studies on DOAC reversal with activated PCC have provided questionable results regarding its safety, particularly in terms of thrombotic effects.[71]

Prothrombin Complex Concentrate in Intracranial Bleeding

Numerous investigations have focused on intracerebral hemorrhage and traumatic brain injury to prevent further hemorrhagic progression in anticoagulated patients receiving oral anticoagulants including VKAs and DOACs. Despite the heterogeneity of study designs, the use of 4F-PCCs for intracerebral hemorrhage in anticoagulated patients is reported with favorable outcomes in terms of INR reversal for VKA-treated patients as well as 30-day mortality and thromboembolic events in oral anticoagulated patients.[72–80] A propensity score–weighted analysis of patients with apixaban- or rivaroxaban-associated intracerebral

hemorrhage found that andexanet alfa demonstrated superior hemostatic efficacy and survival compared to 4F-PCC.[72] However, this effect was not observed in retrospective cohorts of similar patients.[76,77] Other systematic reviews, lacking randomized clinical trials, have failed to demonstrate significant differences in the effectiveness of DOAC reversal in cases of intracerebral hemorrhage.[75] However, a recent randomized controlled trial involving 530 patients with intracerebral hemorrhage on factor Xa inhibitors found that andexanet alfa resulted in better control of hematoma expansion (67% *vs.* 53.1%; adjusted difference, 13.4; 95% CI, 4.6 to 22.2; $P = 0.003$) compared to usual care, which included PCC, emphasizing that both groups achieved effective hemostasis. Nevertheless, andexanet alfa was associated with an increased incidence of thrombotic events (10.3% *vs.* 5.6%; adjusted difference, 4.6; 95% CI, 0.1 to 9.2; $P = 0.048$), including ischemic stroke (6.5% *vs.* 1.5%).[80] In cases of mild traumatic brain injury, the use of 4F-PCC for factor Xa inhibitor–associated intracerebral hemorrhage did not affect the incidence or degree of hemorrhage progression and did not result in an increased rate of thromboembolic events based on retrospective observational data.[73] The efficacy of 4F-PCC in reversing factor Xa inhibitor–related intracerebral hemorrhage was comparable to its efficacy in warfarin-related intracerebral hemorrhage, as demonstrated in a meta-analysis[74] and a subsequent multicenter retrospective cohort study.[78]

Prothrombin Complex Concentrate in Major Trauma Hemorrhage

The indication for tranexamic acid or other procoagulants, such as 4F-PCC, in traumatic bleeding is not mutually exclusive but rather guided by the course of the bleeding, the severity of the patient's condition, and overall clinical status. Treatment should be individualized based on these factors, with ongoing monitoring as appropriate.[47] Because fibrinogen is the most commonly depleted coagulation factor in traumatic bleeding, fibrinogen concentrate or cryoprecipitate is usually used more frequently and in higher amounts compared to 4F-PCC.

The debate on the appropriateness of 4F-PCC *versus* FFP in managing traumatic hemorrhage has long been influenced by geographical location and resource availability.[81–83] In cases of acquired traumatic coagulopathy, 4F-PCC is particularly indicated when endogenous thrombin generation is significantly impaired, highlighting the benefit of a multimodal therapy approach to minimize risks and enhance efficacy.[28,37,44,70,84,85] Observational studies suggest that the early administration of 4F-PCC can boost thrombin generation and reduce the need for allogenic blood product transfusions.[17,86,87] The combination of FFP and 4F-PCC has not been shown to provide additional protection through glycocalyx shedding.[88] New data on resuscitation of massive traumatic bleeding with plasma or factor concentrates are awaited.[89]

A systematic analysis demonstrated an association between the use of PCC in addition to FFP and reduced mortality in trauma-related bleeding in patients not taking anticoagulants (odds ratio, 0.64; 95% CI, 0.46 to 0.88; $P = 0.007$; $I^2 = 0\%$), although the pooled analysis was confounded by heterogeneity and lack of included clinical trials.[53] Another meta-analysis showed that combining PCC with FFP decreased the need for allogenic blood transfusions, improved survival rates, and led to successful clinical outcomes without increasing thromboembolic events compared to FFP alone in TIC patients.[54] However, a later systematic review concluded that the use of PCC was not definitively associated with reduced mortality (odds ratio, 0.94; 95% CI, 0.60 to 1.45; I^2 64%).[24] Despite potential biases in study selection, adjusted analyses indicate a better association between PCC use and reduced mortality in trauma patients (odds ratio, 0.68; 95% CI, 0.51 to 0.90; I^2 0%), emphasizing the need for better discrimination in assessing outcomes to optimize TIC treatments.[55] The heterogeneity observed in the systematic reviews of the use of 4F-PCC in traumatic hemorrhage have failed to find significant differences in the cases in which the inclusion of patients with penetrating *versus* blunt trauma was distinguished.[24]

Robust evidence for clinical use of PCC in severe trauma and the risk of massive transfusion comes from the PROCOAG trial,[48] despite some methodologic limitations. The trial's reliance on PT ratios to define coagulopathy, rather than global coagulation assessments like viscoelastic testing, limits the generalizability of its findings. PT values can indicate a deficiency in procoagulants but do not account for concurrent deficiencies in anticoagulants.[90] Although PT has been used to predict early coagulopathy and guide plasma transfusion in trauma,[40,91,92] it has not been a reliable predictor of perioperative bleeding.[93] The PROCOAG trial hypothesized that combining 4F-PCC with a ratio-based transfusion strategy (packed red blood cells [PRBCs]:FFP ratio of 1:1 to 2:1) would be superior to the ratio-based strategy alone in reducing 24-h blood product consumption. The trial included patients at risk of massive transfusion, defined as those requiring at least 1 unit of PRBC during prehospital care or within 1 h of admission, an assessment of blood consumption score greater than or equal to 2, or those needing 3 units or more PRBCs within the hour of admission or 10 units or more PRBC within 24 h. Of 4,313 admitted patients, 327 were randomized, and 324 were analyzed (160 in placebo group and 164 in the 4F-PCC group). At randomization, about two thirds of the patients had a PT ratio greater than 1.2, and one-quarter had a PT ratio greater than 1.5. Both groups were comparable regarding the need for surgical/interventional hemorrhage control, although more patients in the placebo group received tranexamic acid (86% *vs.* 76%) and a higher median dose of fibrinogen concentrate. The median 24-h blood product consumption was not significantly different between the groups (12 units [5 to 19] in

4F-PCC group *vs.* 11 units [6 to 19] in the placebo group; absolute difference, 0.2 units; 95% CI, −2.99 to 3.33; P = 0.72). However, thromboembolic events (superficial and deep venous thrombosis, pulmonary embolism, stroke, and extremity ischemia) were more frequent in the 4F-PCC group, with 56 patients (35%) experiencing at least one event compared to 37 patients (24%) in the placebo group (absolute difference, 11% [95% CI, 1 to 21%]; relative risk, 1.48 [95% CI, 1.04 to 2.10]; P = 0.03).[48] This study recognizes as a limitation the possible bias of having administered 4F-PCC and FFP together, which would mask a possible excess of procoagulant factors and their influence on the results of thromboembolic events. Among other methodologic limitations, such as the lack of monitoring of thrombin generation deficiency before administration of 4F-PCC and its raw comparative administration *versus* FFP, we must consider all its results as valid but without extrapolating the generalization of a risk of serious adverse effects that would discourage their use in traumatic bleeding. We advocate the development of new randomized clinical trials to contrast these results. Previous studies have explored the effects of FFP-only strategies *versus* FFP plus 4F-PCC,[94,95] and a single-center open-label trial has compared a combination of fibrinogen concentrate, factor XIII, and 4F-PCC *versus* FFP.[17] All of these studies reported reductions in blood product consumption with the administration of 4F-PCC. The ongoing Trauma and Prothrombin Complex Concentrate trial aims to determine whether 4F-PCC can reduce mortality in patients predicted to require large volume of blood transfusions (ClinicalTrials.gov identifier NCT05568888). This trial is expected to provide further insights into the effectiveness and safety of 4F-PCC in trauma settings, potentially influencing future guidelines and clinical practice.

Given the growing use of low-titer O group whole blood resuscitation in the United States, it would be beneficial to promote comparative research in exsanguinated patients to determine which initial resuscitation strategies lead to earlier and more effective hemostasis, better control of coagulopathic bleeding, and improved survival. However, designing such studies would be challenging, because these strategies are inherently different: 4F-PCC primarily focuses on restoring thrombin generation, whereas whole blood serves as a more comprehensive resuscitation product. Careful consideration must be given to these differences when conducting comparative research.

To summarize, based on the available evidence and multidisciplinary guidelines endorsed by organizations such as the European Trauma Guidelines,[47] the use of 4F-PCC is indicated for severe bleeding events in which impaired thrombin generation is confirmed by the loss and/or consumption of coagulation factors, as identified through conventional coagulation analysis or viscoelastic testing. 4F-PCC is not recommended as a first-line empirical treatment, except in cases of exsanguination or very rapid massive bleeding, where rapid replenishment of coagulation factors, along with volume replacement and erythrocyte transfusion, is the primary objective. It is crucial to consider the patient's comorbidities, which may increase the risk of thromboembolic events, and to individualize dosing to avoid overdosage.

Prothrombin Complex Concentrate in Hip Fracture

PCC has been evaluated in urgent scenarios involving frail patients with hip fractures who are on anticoagulant medication.[96] Implementing an anticoagulant protocol has proven effective in decreasing time to surgery without increasing the risk of bleeding. Current evidence suggests that the safe window to perform surgery is within 24 to 48 h.[97,98] Anticoagulant reversal with 4F-PCC in these scenarios appears unjustified unless there is severe bleeding, and waiting times should be adjusted to optimize hemostasis, taking into account quality indicators.

Four-factor Prothrombin Complex Concentrate in Current Trauma Guidelines

Many trauma guidelines do not specifically address the use of 4F-PCC to treat coagulopathy, such as guidelines for pelvic fracture bleeding,[99] pediatric severe traumatic brain injury,[100] and pregnant trauma patients.[101] The application of 4F-PCC is closely linked to POC testing, goal-directed treatment algorithms, and the availability of medications, resulting in regional variations in recommendations. The European guidelines on the use of PCC in trauma are summarized in table 1.[47,102–108] Most of these guidelines do not specifically mention 4F-PCC in their general recommendation, and this generalization is reflected in table 1.

Summary

The indiscriminate use of 4F-PCC in trauma-induced coagulopathy is not advisable due to potential thrombotic risks and limited impact on mortality. Nonetheless, 4F-PCC is increasingly used in trauma patients with major bleeding, TIC, oral anticoagulants, or traumatic brain injuries. For urgent DOAC reversal, both 4F-PCC and specific antidotes are effective. Andexanet alfa, although associated with higher thrombotic risk, has shown superiority in cases of intracranial hemorrhage.

High-quality evidence for unrestricted 4F-PCC use in adult trauma is limited, with studies being heterogeneous regarding patient populations, drug formulations, and comparator selection. Most studies are retrospective and observational. The diagnosis and monitoring of TIC are challenging due to the need for rapid and broad availability of diagnostic tools. PT and INR, despite being influenced by various factors, remain the most common tests. Viscoelastic POC tests suggest a focus on restoring thrombin generation, with EXTEM CT (or R in TEG) being more suitable for assessing thrombin generation and plasma coagulation status. The concurrent use of different PCC

Table 1. Summary of Recommendations of PCC in European Guidelines

Guideline	Main Statement on PCC	Class of Recommendation and Evidence Level
European Trauma Guideline (6th Edition)[47]	We recommend the early and repeated monitoring of hemostasis, using either a traditional laboratory determination such as prothrombin time/international normalized ratio, Clauss fibrinogen level and platelet count, and/or point-of-care prothrombin time/international normalized ratio and/or a viscoelastic method	1C
	Provided that fibrinogen levels are normal, we suggest that PCC is administered to the bleeding patient based on evidence of delayed coagulation initiation using viscoelastic testing	2C
	In the bleeding trauma patient, we recommend the emergency reversal of vitamin K–dependent oral anticoagulants with the early use of both PCC and 5–10 mg IV phytomenadione (vitamin K_1)	1A
	If andexanet alfa is not available or in patients receiving edoxaban, we suggest the administration of PCC (25–50 U/kg)	2C
German Trauma Guidelines[102]	Recommend PCC in patients with life-threatening bleeding and/or in shock, in addition to fibrinogen	NA
Spanish "Seville document"[103]	Suggests PCC for coagulopathic trauma patients	NA
HEMOMAS document[104]	Prefers fresh frozen plasma over PCC in massive bleeding and limits PCC if risk of transfusion-related acute lung injury or transfusion acute cardiac overload	NA
European Expert Meeting[105]	Allows PCC use in expected coagulation factor deficiency	NA
Association of Anaesthetists of Great Britain and Ireland[106]	Recommends PCC for vitamin K antagonist reversal in trauma victims	NA
British Society of Haematology[107]	Does not suggest the use of PCC in trauma patients outside a clinical trial	NA
European Guideline on reversal of direct oral anticoagulant in patients with life threatening bleeding[108]	If idarucizumab not available in patients on dabigatran and severe bleeding, PCC or activated PCC is suggested	2C
	PCC or andexanet alfa should be considered in patients under activated coagulation factor X inhibitor therapy with severe bleeding	1C
	Andexanet alfa or PCC are suggested to prevent increasing hematoma volume after apixaban and rivaroxaban-associated intracerebral bleeding	2C
	If andexanet alfa or PCC are not available, activated PCC may be considered	2C

NA, not available; PCC, prothrombin complex concentrate.

formulations in studies complicates comparisons, as 3F-, 4F-, and activated PCCs have distinct compositions and should be considered separate drugs.

Current literature should be interpreted cautiously due to these methodologic variances. Further prospective studies and randomized controlled trials are urgently needed to compare the efficacy and safety of 4F-PCC with other strategies, such as whole blood or FFP transfusion, and to evaluate DOAC reversal with specific antidotes *versus* 4F-PCC in trauma-related major bleeding.

Appropriate patient selection, a thorough understanding of the pathophysiology, and the highly dynamic nature of traumatic bleeding are key to optimizing the successful use of 4F-PCC in clinical practice. Prioritizing the restoration of documented thrombin generation deficits, as identified through viscoelastic or conventional coagulation assays, will provide more precise guidance. In cases of severe thrombin deficiency due to rapid and massive blood loss, 4F-PCC is likely to be an effective option. However, the choice of therapy should always consider factors such as availability, risk-benefit analysis, resources, and the urgency of the clinical situation.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

Dr. Mora received honoraria for consulting from Octapharma (Lachen, Switzerland) and Grifols (Los Angeles, California). Dr. Maegele received honoraria for lectures and participation in expert/advisory board committees and financial support for participation in congresses and scientific projects from Abbott (Abbott Park, Illinois), Astra Zeneca (Cambridge, United Kingdom), Baxter (Deerfield, Illinois), Bayer (Leverkusen, Germany), Biotest (Dreieich, Germany), CSL Behring (King of Prussia, Pennsylvania), IL-Werfen/TEM International (Munich, Germany), LFB Biomedicaments France (Les Ulis, France), Portola (South San Francisco, California), and Octapharma. Dr. Grottke has received research funding from AstraZeneca, Alexion (Boston, Massachusetts), Alvereon (Nijmegen, The Netherlands), Bayer AG, Biotest, Boehringer Ingelheim (Ingelheim am Rhein, Germany), CSL Behring, Octapharma, Novo Nordisk (Copenhagen, Denmark), Nycomed (Zurich, Switzerland), Portola, Werfen (Barcelona, Spain), Federal Ministry of Education and Research (BMBF; Bonn, Germany), and German Research Foundation (DFG; Bonn, Germany); he has also received honoraria for lectures and consultancy support from AstraZeneca, Baxalta (Tokyo, Japan), Bayer AG, Boehringer Ingelheim, Ferring (Saint-Prex, Switzerland),

CSL Behring, Octapharma, Pfizer (New York, New York), Takeda (Tokyo, Japan), Portola, Sanofi (Paris, France), and Werfen. Dr. Levy is on the advisory committees for Bayer, Grifols, Octapharma, Takeda, and Werfen. The other authors declare no competing interests.

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