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Review

Prothrombin Complex Concentrates in Post-traumatic Hemorrhage: A Review

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ABSTRACT

Prothrombin complex concentrates (PCC) has long been used to reverse vitamin K antagonists (VKA)-induced coagulopathy rapidly and safely. However, its use in trauma-induced coagulopathy (TIC) in patients not using VKA drugs is yet to be elucidated. This article is a narrative review and analysis of the most recent literature to analyse consequences, and intended effects associated with this treatment modality in TIC. Utilization of PCC was addressed in the literature data found by searches of databases. The indications, efficacy and outcomes associated with the use of the product were reviewed in the articles. Some studies point out promising results with respect to PCC use to overcome the VKA-related coagulopathy in victims of trauma. PCC may be a viable option for resuscitation in emergency and critical care in the management of severe hemodynamic deterioration induced by trauma, despite contradictory findings in the literature.

Keywords
Blood coagulation factor; Trauma; Hemorrhagic shock; Exsanguinating hemorrhage.

PROTHROMBIN COMPLEX CONCENTRATES FOR TRAUMATIC HEMORRHAGE

Trauma is an everlasting challenge to public health worldwide, and hemorrhage is the most common cause of potentially preventable death among victims of trauma. More specifically, one in every two deaths within the first day following injury result from hemorrhage and hemorrhagic shock can lead to post-resuscitation organ failure and related mortality.[1]

Acquired deficiencies related to coagulation cascade are also blamed for the death toll among patients exposed to traumatic injuries. Alterations in prothrombin time (PT) and partial thromboplastin time (PTT) in trauma victims were described first in 2003.[2,3] These disturbed levels in laboratory correlated with increased mortality and effectively changed the approach to trauma care nowadays.

Contemporary damage control resuscitation encompasses ratio-based transfusion of packed red blood cells, plasma and platelets. Although this approach is still viewed as the "gold standard" of trauma care, goal-directed algorithms directed by coagulation tests or viscoelastic studies may allow a better definition of any given patient's coagulopathy.[4] This strategy will allow a more individualized and targeted treatment modality. Prothrombin complex concentrate (PCC) are also advocated in many types of coagulopathy, especially those induced by drugs such as vitamin K antagonist (VKA) and direct oral anticoagulants.

The objective of this research is to highlight the usage characteristics and effects of PCC in trauma-induced coagulopathy (TIC). This article is a review and analysis of the most recent literature to analyse consequences, and intended effects associated with this treatment modality in TIC.

## PROTHROMBIN COMPLEX CONCENTRATES: THE HISTORY AND BACKGROUND

PCC is mostly used to mitigate effects of acute overdose of VKA. Patients with major bleeding while taking VKA-therapy eventually diagnosed with acute overdose of VKA-require rapid reversal of life-threatening coagulopathy. PCC was at first developed to treat hemophilia, the agent is now used for the expedient reversal of untoward high-levels of international normalized ratio (INR).[5]

Structure and Chemical Properties

Two types of PCC are available, the 3-factor and the 4-factor PCC. Literature data support that the 4-factor PCC has greater amounts of factor VII in conjunction with proteins which possess anti-coagulant properties (protein-C, Antithrombin, and heparin) than the 3-factor PCC.[6] Four-factor PCC was suggested as the main element of the treatment strategy of VKA-induced bleeding by the current guidelines.[7,8] Furthermore, there are concrete data from animal and human studies suggesting that 4F-PCC may have similar efficacy in relieving coagulopathy associated with the factor X_a inhibitors apixaban and rivaroxaban.[9,10] Likewise, Harrison et al demonstrated that in patients with direct oral anticoagulant and VKA-associated intracranial hemorrhage treated with 4F-PCC had similar outcomes, without any thromboembolic adverse events.[11]

Etiology and Pathophysiology of "Trauma-Induced Coagulopathy" (TIC)

Tissue damage and hemorrhage during trauma leads to shock, which, in turn, prompts hypoperfusion and systemic endotheliopathy (i.e., inflammation, platelet activation, reduced clotting factor activity, sympathoadrenal activation, and hyperfibrinolysis) (Figure 1).

Figure 1. *Pathophysiology of Traumatic Coagulopathy*
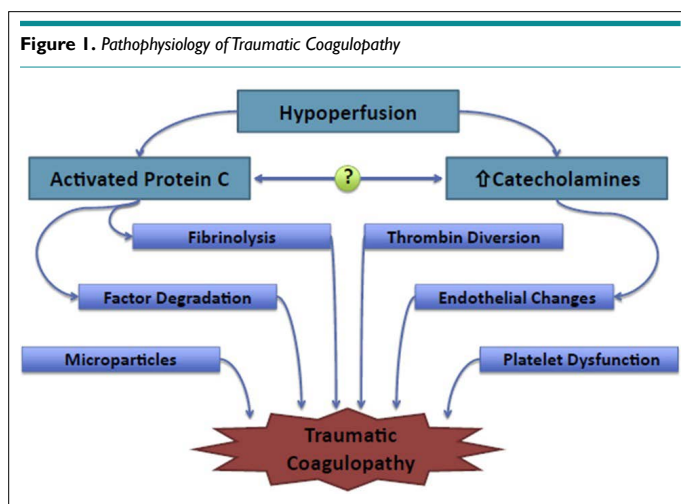
The term "acute traumatic coagulopathy" refers to an endogenous entity, including all components of hemostasis that are triggered by tissue injury, hypoperfusion and shock and pa view the way to coagulation disorder in these patients.[4] On the other hand, the consequences of shock are also affected by resuscitation-associated factors such as dilution of coagulation factors, hypothermia and acidosis, and also by trauma-associated factors including loss of coagulation factors.[12] All of these effects culminate to trigger TIC as a multifaceted syndrome threatening many lives at any given time worldwide (Table 1).

Table 1. *Pathophysiologic Processes Involved in Traumatic Coagulopathy*

- Endothelialdys function: elevated circulating levels of Syndecan-1 (a protein normally found in theglycocaly x of the endothelium)
- Impaired platelet function
- Relative thrombocytopenia
- Microparticles: Thrombin-richmicroparticles, Circulating endothelial-, Erythrocyte-, Andleukocyte-derived microparticles

Kutcher et al reported a posttraumatic platelet dysfunction accompanied by a normal platelet count and standard clotting studies, with substantial implications for mortality. Multiple electrode impedance aggregometry accurately identified this dysfunctional platelets in trauma cases, and admission arachidonic acid and collagen responsiveness were found to be specific independent predictors of mortality.[13]

One-fourth of critically injured trauma patients are coagulopathic on arrival, increasing to close to 100% after receiving a massive transfusion.[14,15] TIC is recognized to be a grave indicator, with greater transfusion need, higher levels of organ dysfunction, and a 4-fold increase in mortality.[2,16] TIC also leads to poor outcomes with higher transfusion requirements; increased multiorgan system failure, increased hospital, intensive care, and ventilator days; and boosted death toll.[17,18]

Evaluation of Trauma with Special Emphasis on TIC

Initial assessment of any trauma victim with bleeding should include exploration of traumatic haemorrhage taking patient's physiology, anatomical injury pattern, mechanism of injury and the patient response to initial resuscitation into account (Grade 1C).[12] The shock index (SI) can be used as well, to assess the degree of hypovolaemic shock. (Grade 2C). Coagulopathy is encountered in every third of trauma victims.[2,3,16]

Acute blood loss and resultant anemia associated with traumatic hemorrhage can impair the clotting mechanism as well, since anemia may render platelet marginalization more difficult thus slowing platelet activation.[12] Kutcher et al demonstrated that almost half of patients with serious injuries on presentation and more than 90% of patients at five days exhibited platelet dysfunction by multiplate impedance aggregometry.[13] Interestingly, these patients can still have normal platelet counts. They also noted that platelet dysfunction on presentation was predictive of death in patients with multiple trauma.

Coagulopathy in trauma patients can be attributed to the traumatic damage or treatment effect of VKA. Balanced resuscitation is the essential strategy in those with TIC, but optimized ratios for resuscitation and monitoring protocols for transfusion are yet to be elucidated.[19] In a very recent review, Harris et al cited that the current understanding of TIC is evolving and may see targeted blood component therapy incorporated early in trauma shock

resuscitation.[20] In another review, Cohen et al postulated that those with TIC had grave outcomes with transfusion rates, infection, thromboembolism, acute lung injury, organ failure, and mortality.[19]

Coagulopathy is demonstrated to have resulted in a substantially greater fatality rate in those patients with acute injuries.[3] Recently, the strategy of "damage control resuscitation (DCR)" which encompasses expedient use of blood products with a greater ratio of packed red blood cells to FFP to platelets than the previous regimes is being used.[21,22] This has been thought to lower the incidence of coagulopathy.[22,23] Meanwhile, FFP and platelets were claimed to hasten the risks of volume overload and infections attributed to the transfusion of blood product.[24,25] Likewise, Watson et al demonstrated that the potentials of acute lung injury is the greatest following FFP administration.[24]

Matsushima et al reviewed the literature in 2015 and reported that there are small researches that put forth promising findings with regard to PCC utilization to overcome the VKA-related coagulopathy in trauma victims.[26] It remains to be answered if PCC can be a remedy in patients in need of massive transfusion.

Uncontrolled hemorrhage including TIC is still among the prominent factors underlying preventable death after trauma, and expedient diagnosis and aggressive management accompany inarguably better outcomes.

Current treatment concepts include the DCR concept, which advocates the empiric administration of blood products in predefined ratios and the concept of 'Goal-directed Coagulation Therapy' (GDCT) based on findings elicited from point-of-care testing.

GDCT based upon viscoelastic testing allows better characterization of the coagulopathy with supplementation of hemostatic agents and blood products according to the individual patient's needs.[27]

HOW MUCH FLUID TO GIVE?

At first, a substantial amount of crystalloids is to be administered as a fluid challenge to the victim. Then, the response to this challenge should be criticized in the context of small-volume resuscitation and "permissive hypotension", which is recommended in the trauma patients with hemorrhage. Permissive hypotension with a target systolic pressure of 80 to 90 mmHg –in conjunction with a mean arterial pressure of 50 to 60 mmHg –till bleeding is halted expediently after trauma without brain injury is a major strategy (Grade 1C).[12] In other circumstances, a Hb level of 7 to 9 g/dL can be targeted (Grade 1C). There is no evidence to support permissive hypotension as the main strategy in pediatric severe trauma. Therefore, permissive hypotension in trauma is not applicable to pediatric cases, which are defined as those under 15-years of age.

Imaging Studies to Guide Resuscitation

Focused assessment with sonography in trauma (FAST) ultrasound for the identification of –mostly abdominal– free fluid in patients with trauma. (Grade 1C). Ultrasound should also be viewed as a useful point-of-care guide for fluid deficits or responsiveness.

Multislice computed tomography (MSCT) allows physicians to be capable of timely diagnosis and expedient management of the patient with multiple injuries. Holstein et al pointed out that a Hb level lower than 8 g/dL in patients with pelvic trauma was associated with mortality.[28]

Lactate levels on presentation are an important guide to therapy. The most commonly used cut-off point is 2 mmol/L and normalization of a high-level in a reasonable time (e.g., 24-hours) is an independent predictor of survival.

Fibrinogen in Trauma

Currently, it is a well-known fact that a reduction in blood fibrinogen levels are noted in up to two in every five hypotensive trauma victims.[29,30] Schlimp et al postulated that presentation fibrinogen levels of major trauma patients have strong correlation with rapidly obtainable, routine laboratory parameters such as hemoglobin and base excess.[30] Therefore, fibrinogen is viewed as a key ingredient of multiple trauma treatment protocols.[31]

Treatment of Posttraumatıc Coagulopathy

Nowadays, the only therapy supported by concrete evidence in patients with TIC is tranexamic acid (TXA) acting as an antifibrinolytic in order to decrease resultant death toll.[32-35] Furthermore, TXA is usually given empirically because there are suspicion about the accuracy of diagnostic workup to address hyperfibrinolysis in victims of trauma.[36]

CRASH-2 trial (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage), pointed out that management of bleeding trauma cases with TXA leads to a more favorable outcome. In combat casualties, empiric use of TXA showed the greatest benefit observed in patients who subsequently required a massive transfusion.[33]

In the treatment of posttraumatic coagulopathy, there are two different modalities recommended which follow:

a. Damage control resuscitation approach, which encompasses the empiric administration of blood products and hemostatic agents in predefined ratios or

b. A targeted approach directed by bedside viscoelastic studies. Current data suggest that a ratio of pRBCs: plasma: platelets of 1:1:1 in massive transfusion may be favorable along with improved outcomes.

DO WE NEED TO INFUSE PCC TO THIS PARTICULAR PATIENT?

In 2017, Balendran et al researched on a point-of-care prothrom-

bin time test (POC PT) as a more practical option in detecting those with reduced prothrombin activity.[37] They concluded that the test represented a fast, simple, and mobile technique to guide PCC or Recombinanthuman prothrombin (MEDI8111) therapy in bleeding victims of trauma. Although the study is now limited to preclinical phase, it can provide the rationale for future clinical validation of the test to support MEDI8111 development and future clinical use in the management of trauma.

Effect of PCC in TIC

Exsanguination is the most widespread cause of death in trauma.[38] Replacement of factors is essential in the correction of TIC. For a long time, FFP is being used to mitigate the effects of TIC in the acute setting.

Jehan et al conducted a retrospective analysis of prospectively maintained database of coagulopathic trauma patients to compare 4-PCC+FFP *vs.* FPP alone for the treatment of TIC.[39] They reported that FFP is associated with the rapid reversal of INR (373 *vs.* 955 min; *p*=0.001) and reduction in transfusion requirements as compared to FFP alone. The component therapy of 4-PCC also resulted in a reduction in pRBC units (7 *vs.* 9 units; *p*=0.04), and FFP units (5 *vs.* 7 units; *p*=0.03) transfused than in those managed only with FFP. 4-PCC as a component therapy along with FFP is superior to FFP alone for the reversal of TIC. PCC is included in the advocated strategy for the acute reversal of VKA-effect in the European guidelines on the management of perioperative and posttraumatic hemorrhage.[12]

Baskaran et al cited that PCC has an off label use in the setting of trauma with massive transfusion.[40] Some studies have shown better INR reduction with PCC+FFP compared to FFP alone.[41]

It is important to remember that PCC does not contain factor V and may not be sufficient as a single agent in traumatic causes requiring massive transfusions.[40] Many prospective clinical researches have linked early TIC to protein-C depletion (activated protein-C elevation), and boosted potential of acute lung injury, ventilator-associated pneumonia, multisystem organ failure, and death.[18,42]

Thromboelastometry (TEM) is useful to guide individualised goal-directed coagulation therapy in patients with traumatic coagulopathy.[43,44]

Head Injury

The usefulness of PCC has been demonstrated, with evidence of reduced haematoma formation in patients with head injury,[45,46] and is preferable to FFP for the rapid reversal of the effects of VKAs.[47-49]

ANY DRAWBACKS?

The propensity of thrombosis-related disorders attributed to infu-

sion of PCC should be weighed against the necessity for expedient reversal of coagulopathy.[50] Of note, thromboembolic events are encountered more frequently in trauma patients with the administration of 3-F PCC than with 4-F PCC.[51]

The risk of thrombosis may be more substantial with the use of "activated PCC" (aPCC) as compared to non-activated PCC[52] due to the presence of activated factor IX, because the PCC infusion precipitates thrombogenicity at the level of factor X activation as an ingredient of aPCC.[53]

Alternative Agents in the Treatment of TIC

The routine use of TXA in the posttraumatic hemorrhagic shock was not been sufficiently evidenced for robust recommendations.[54] Porta et al investigated the efficacy of TXA and PCC on TIC with a severe metabolic acidosis and compare the efficacy of PCC versus FFP to reverse a dilutional coagulopathy.[55] They noted that TXA and PCC appear to act favorably in correcting TIC *in vitro*, and TXA had no loss of function in metabolic acidosis.

Safety Issues

The safety of PCC has been studied by many researchers for the recent decades. Thrombotic events are recognized as the main adverse effects of the treatment and have been postulated to increase in patients treated with higher doses PCC.[56]

Dosing Issues

PCC formulations used by different brands have a major issue of being non-standardized. Different sources of PCC are standardized based on factor IX levels. The main concern is their compositional differences whose effect on the outcomes are not established clearly.[57] Some sources of PCC supply a low level of factor VII, which are called 3 F-PCC. These 3 F-PCC are thought to be less efficacious in the treatment of VKAIC.[58]

Khorsand et al performed a systematic review to describe the currently used PCC dosing strategies and to present their efficacy.[59] They found no evidence that one dosing strategy is superior. Huynh et al. compared PCC doses of 35 IU/kg with low-dose (25 IU/kg) in correction of their first INR less than 1.5 in adult patients with warfarin-associated traumatic brain injury.[60] Moderately dosed PCC (35 IU/kg) was associated with a higher percentage of INR reversal, compared to the treatment with a lower dosage of 25 IU/kg in this group of trauma victims.

Recently, Abdoellakhan et al examined a fixed 1000 IU fIX PCC dosing protocol for ICH, in comparison to a variable dose approach to achieve an INR B 1.5.[61] The fixed-dose protocol necessitates additional PCC infusions more frequently to achieve the target INR. They concluded that implementation of a fixed dose of 1000 IU fIX cannot be recommended for VKA-related ICH.

Use in Traumatic Brain Injury and ICH

Annually almost 1% of all VKA users develops an intracranial hemorrhage (ICH).[62] Most guidelines from developed countries recommend administration of 4-F PCC to reverse VKA-therapy in ICH. These recommendations are deprived of consensus on PCC doses or the target INR to be achieved.[63]

Steiner et al assessed the safety and efficacy of FFP versus PCC in patients with VKA-ICH.[64] In patients with VKA-ICH, 4F PCC can act more favorably than FFP in improving the INR, which appears to be linked with slower enlargement of haematomas. It is also known that the efficacy of PCC on clinical outcomes are yet to be proven, despite the available data are in favor of the utilization of PCC over FFP in intracranial haemorrhage related to VKA. Likewise, PCC provides a much more rapid reversal of coagulopathy than standard treatment with only FFP and vitamin K in geriatric trauma patients with ICH.[45]

Comparison of PCC with FFP

PCC has practical and theoretical advantages to FFP, as it can be used more rapidly and it does not warrant to be thawed or cross-match of blood groups. Goldstein et al compared the efficiency and safety of 4-F PCC with that of FFP in 181 patients with VKAIC who underwent urgent surgical or invasive procedures.[48] They wrote that 4F-PCC is better than plasma for rapid INR reversal and effective haemostasis in those needing VKA reversal before surgical or invasive procedures (Table 2).

Table 2. *Properties of Prothrombin Complex Concentrates (Pcc) and Fresh Frozen Plasma (Ffp) Derived from Published Data so Far*

	PCC	FFP
Feasibility-ease of use	+++	+
Cost-effectiveness	+++	+
Volume loading	Loads less volume	Loads more volume
Onset of efficacy	Sooner	Later
INR reversal	Morerapid	
Time taken for completion of treatment	Morerapid	
Cardiopulmonary Adverse effects	None	

CONCLUSION

PCC compounds has long been used to reverse coagulopathy following use of VKA. However, its use in TIC in patients not using VKA prescriptions has not been clarified. Some literature data yielded promising results with respect to PCC use to overcome the VKA-related coagulopathy in victims of trauma.

PCC may be a viable option for resuscitation in emergency and critical care in the management of severe hemodynamic deterioration induced by trauma. PCC has practical and theoretical advantages to FFP, as it can be used more rapidly and it does not warrant to be thawed or cross-match of blood groups. TEM can be used to guide individualised therapy in patients with TIC. The indications, efficacy and outcomes associated with the use of PCC in the setting of trauma including scenarios involving pure ICH and multiple trauma are yet to be thoroughly revised.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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