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Reversal Of Warfarin-Associated Coagulopathy: Prothrombin Complex Concentrates Versus Fresh Frozen Plasma In Elderly Patients Presenting With Intracranial Hemorrhage

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Abstract

Background: Patients on warfarin with traumatic intracranial hemorrhage (ICH) often require pharmacological reversal of warfarin-induced coagulopathy. We compared outcomes among patients who received 4-factor prothrombin complex concentrate (PCC), fresh frozen plasma (FFP) or no reversal to assess the real-world impact of PCC on elderly patients with traumatic intracranial hemorrhage on warfarin.

Study Design: This was a retrospective analysis of 150 patients on preinjury warfarin. Data was abstracted from the electronic medical record (EMR) of an academic level 1 trauma center for patients age 65 years and greater on warfarin therapy admitted with a traumatic ICH between January 2013 and December 2018. Primary outcomes were ICH progression on follow-up computed tomography (CT) scan, in-hospital mortality, need for surgical intervention. Trends in use over time and costs of the reversal agents were also analyzed.

Results: Of 150 patients eligible for analysis, 41 received FFP, 60 received PCC, and 49 were not reversed with either of those reversal agents. On multivariable analysis, patients who were not reversed [OR 0.25, 95% CI (0.31 – 0.85)] or were female [OR 0.38, 95% CI (0.17 – 0.88)] were less likely to experience progression of their initial bleed on follow-up CT. SDH increased the risk of hemorrhagic progression [OR

3.69, 95% CI (1.27 – 10.73)]. There was no difference between groups with respect to in-hospital mortality or the need for neurosurgical intervention. Over time, the use of reversal with PCC increased, while use of FFP and not reversing declined ($p < 0.001$). Regarding costs, PCC was significantly more expensive to administer per patient than FFP.

Conclusion: In older patients with traumatic ICH on warfarin, use of a reversal agent was associated with progression of the ICH. The choice of reversal agent did not impact mortality or the need for surgery. Therefore, some ICH patients may not require warfarin reversal, and the apparent benefits to PCC use in retrospective studies may be related to the increased use of PCC in patients who would have not have otherwise been reversed.

Introduction

The Case for Anticoagulation Therapy

Hypercoagulable states are associated with many adverse outcomes, including disabling stroke and deadly pulmonary emboli (PE). Other common pathologies that predispose patients to poor outcomes related to blood clotting are atrial fibrillation (AF) and venous thromboembolism (VTE), the latter of which includes deep venous thrombosis (DVT) and PE. Due to the significant vascular risks, AF and VTE are significantly associated with increased morbidity and mortality. Therefore, medical management becomes crucial in controlling overall prognosis.

AF is caused by an underlying cardiac abnormality that leads to uncoordinated atrial arrhythmias and irregular ventricular responses. Inflammation and fibrosis within the cardiac tissues, valvular abnormalities, or even an ectopic signal arising within the pulmonary veins can all be underlying causes of this abnormal atrial rhythm. With the loss of coordinated atrial contractions comes a decrease in adequate ventricular filling and stroke volume. While some cases of AF are asymptomatic and therefore clinically silent, more severe manifestations can include dyspnea, palpitations, and pulmonary edema [1], as the heart becomes unable to propel blood systemically. Additionally, the loss of forward blood flow means more blood is static within the heart, which contributes to an increased risk

of intracardiac thrombus formation. Dislodgement of these thrombi can then lead to stroke [2].

AF is the most common clinically significant cardiac arrhythmia in the world, with an estimated global burden of 33.5 million people [3]. In the United States alone, approximately 2.3 million people have a diagnosis of AF, with that number being projected to increase to 5.6 million by 2050 due primarily to a substantial increase in the elderly population, who develop AF in greater numbers than their younger counterparts. In the United States, AF is more often seen in elderly, Caucasian men, and can affect anywhere from 8 – 10% of people over 80 years old [4]. In fact, the prevalence of AF doubles with each increasing decade of age [5]. AF incurs a four-to-fivefold increased risk of stroke, and has been estimated to be responsible for up to 15% of all strokes nationwide [6]. Due to both the high prevalence and significant stroke risk, AF is the most common dysrhythmia treated in medical practices, and is responsible for up to a third of hospital admissions associated with dysrhythmias [5], making it a significant clinical burden in the healthcare realm.

VTE is another significant condition caused by an underlying pathology in the coagulation cascade that leads to the inappropriate formation of clots within the vasculature. DVT refers to the formation of clots within the deep veins, most often those of the lower limbs and the pelvis. Also included under the category of VTE are PE, which are due to dislodged thrombi that travel within the venous system and become fixed in the pulmonary vasculature. DVT is a significant risk factor for

the development of PE: nearly half of all patients with untreated DVT can develop a PE in as little as 3 months [7]. Acquired risk factors that are known to contribute to an increased risk of VTE development include advanced age, immobility, recent surgery, obesity [8], hormone replacement therapy [9], and malignancy [10]. Genetic conditions, albeit rarer, are also important to consider as underlying causes of VTE development. These conditions are linked to either decreased levels of or inadequate responses to the body's natural anticoagulants, and include Factor V Leiden, prothrombin G20210A, and inherited deficiencies in proteins C, S, and/or antithrombin [8].

VTE is the third most common acute cardiovascular disease after myocardial infarction (MI) and stroke. The condition affects a large portion of the U.S. population with an incidence rate ranging between 300,000 – 600,000 new cases per year. VTE also disproportionately affects the elderly, with nearly 60% of all cases occurring in patients over 70 years old [11]. The mortality rate is significant: up to 30% of patients die within 30 days of diagnosis, and as high as 25% of PE cases alone present as sudden death. Even with appropriate medical management, nearly one third of all patients can experience a recurrence of VTE within 10 years, with a "definite" recurrence rate of 17.6% and a "probable" rate of 30.4% [12].

With such significant morbidity and mortality associated with these disease states, pharmacological management becomes key in improving outcomes. Anticoagulation therapy has been a mainstay of the medical regimen for these conditions for decades. One important and popular therapy that has had significant

benefit in targeting the coagulative sequelae associated with AF and VTE is warfarin, an oral anticoagulant with a mechanism of action that works by preventing the activation of several coagulation factors necessary for clot formation. From its discovery in 1933 [13] to its approval for stroke prevention in AF patients by the Federal Drug Administration (FDA) in 1954 [14], warfarin use has exploded over time, with nearly 30 million prescriptions for the medication now written annually in the United States [15]. In the following section, we will begin to explore both the benefits as well as the adverse effects associated with warfarin use when managing these hypercoagulable conditions.

Benefits and Dangers of Warfarin

Warfarin is in a class of medications known as the vitamin K antagonists (VKAs). VKAs work by inhibiting the enzyme vitamin-K epoxide reductase [16], which is responsible for the post-translational carboxylation of multiple factors necessary in the coagulation cascade. These include factors II, VII, IX, X, as well as proteins C and S [17]. Inhibition of this step results in the inactivation of these factors and creates an antithrombotic effect that counteracts the prothrombotic state seen in conditions like AF and VTE.

Multiple trials have proven the clinical benefit to warfarin use in stroke prevention for patients with nonvalvular AF. The 1990 study by the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) investigators found an 86% reduction in stroke risk in patients receiving long-term, low-dose warfarin therapy

compared to control patients who did not receive warfarin but who could choose to take aspirin [18]. In the 1991 Stroke Prevention in Atrial Fibrillation (SPAF) randomized trial, warfarin was found to significantly reduce the rate of ischemic stroke and systemic embolism when compared to placebo, with an overall 54% reduction in disabling ischemic stroke or vascular deaths in those patients who received the medication [19]. The 1992 Veterans Affairs Stroke Prevention in Nonvalvular Atrial Fibrillation (SPINAF) study was another randomized trial that found warfarin was associated with a 0.79 relative reduction in cerebral infarction risk compared to placebo [20].

Additional studies directly compared the benefits of warfarin to another popular antithrombotic medication, aspirin, which was considered to be the gold standard antiplatelet for the prevention of arterial thromboses [21]. These further studies also found significant benefits to warfarin over aspirin therapy in preventing stroke in AF patients, including the European Atrial Fibrillation Trial (EAFT) [22] and the SPAF II trial [23]. Given the ample evidence for warfarin's clinical benefit in reducing thromboembolic risk in AF patients, it becomes clear why for years the American Heart Association, American College of Cardiology, and Heart Rhythm Society (AHA/ACC/HRS) guidelines consistently included warfarin as a class I recommended pharmacotherapy for antithrombotic AF management [24]. Of note, warfarin was eventually overtaken by the non-vitamin K anticoagulants (NOACs) in January 2019 as the preferred therapy for stroke prevention in AF

patients following the publication of several seminal randomized trials [25], yet this particular topic is beyond the scope of this paper.

Similarly, VKAs have long been a staple in the medical management of VTE. The earliest landmark randomized control trial in 1960 investigating the use of VKAs for treatment of PE found that patients who received heparin and the VKA coumarin-derivative nicoumalone (of note, warfarin is also a coumarin derivative) had a significant reduction in mortality attributed to PE compared to the untreated control group: 0% vs. 26% [26]. Today, VKAs, primarily warfarin, are recommended as long-term secondary prophylaxis following a VTE event following the initial regimen of IV thrombolytics and/or heparin [27].

There is strong evidence linking the use of VKAs to reduced VTE recurrence rates, a finding with great clinical significance given that 10-year VTE recurrence rates can reach levels as high as 30% [12]. In one trial, patients with acute DVT treated initially with intravenous (IV) heparin were randomized to receive either fixed, low-dose subcutaneous heparin or warfarin sodium as secondary prophylaxis. The total recurrence rate after 12 weeks of follow-up was 47% in the heparin group, as opposed to 0% in the warfarin group [28]. One trial went further, and followed 508 patients for an average of 4.3 years, all of whom had previously received 6.5 months of full-dose anticoagulation therapy for VTE. The patients were randomized to receive either long-term, low-intensity warfarin or placebo. The researchers found a significant risk reduction of 64% for recurrent VTE in the therapeutic group relative to the placebo group. Long-term warfarin use was also

found to be associated with a 48% reduction in the overall composite endpoint of recurrent VTE, major hemorrhage, or death [29].

Warfarin has many potential clinical uses beyond AF and VTE. These include warfarin use for the primary prevention of ischemic coronary events as an adjunct to aspirin, as long-term treatment for patients with acute MI, as an antithrombotic in patients with prosthetic heart valves, and even for other less well-supported indications, such as AF due to valvular (as opposed to nonvalvular) heart disease, mitral stenosis, dilated cardiomyopathy, and in patients with one or more episodes of systemic thromboembolism [30]. Altogether, warfarin has proven to be a highly effective anticoagulant for a variety of clinically relevant indications, which explains its vast use among medical practitioners for patients with thromboembolic conditions. However, finding the appropriate balance between antithrombotic activity and the innate risk of bleeding that comes with any anticoagulative medication, especially when considering long-term therapy, can be difficult to achieve. Excessive, systemic anticoagulation with VKAs can lead to bleeding so severe as to prompt rapid, pharmacological reversal in order to prevent catastrophic and fatal hemorrhage. Despite its benefits, warfarin use can be as dangerous as the thrombotic complications it works to prevent if its use is not carefully monitored by patients and care practitioners alike.

Bleeding associated with warfarin use is a serious medical complication, and there is a myriad of factors to be aware of that can increase this risk. These include increasing age, a history of uncontrolled hypertension (HTN), acute or chronic

alcohol use, liver disease, active or a recent history of bleeding lesions or bleeding disorders, and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and some antibiotics [31]. Of the non-modifiable factors, the general consensus is that increasing age is the major risk factor that increases bleeding risk [31].

However, another significant risk factor for warfarin-associated bleeding that has been heavily reviewed in the literature is poor control of the International Normalized Ratio (INR), which is a quantitative measure of the time it takes for clot formation to occur in a measured sample of plasma. Since its introduction in the 1980s [32], INR has become the test of choice to monitor patients on VKAs, and the VKA dose is considered adequate if the INR is within a "therapeutic" range. These exact recommended values vary depending on the underlying clinical pathology being treated with VKA therapy, but typically ranges between 2.0 – 3.5 [33]. An elevated INR outside of the therapeutic range might signify that the dose of anticoagulant is too high, which can translate to an increased risk of bleeding [34]. Several studies have shown that bleeding rates in patients taking warfarin increases with higher presenting INR values [35] [36]. INR can therefore be a reliable predictor for bleeding risk in warfarin patients.

Up to 20% of patients on warfarin will experience a bleeding complication due to excessive anticoagulation per year, and the fatality rate from such bleeds can range between 1 – 3% [37]. In a study investigating rates of hemorrhage in AF patients specifically, bleeding risk was found to be the highest during the first 30 days of warfarin therapy, while the cumulative incidence of associated hemorrhage

increased over time to a value of 8.7% at 5 years following initiation of therapy. Patients older than 75 years of age were at significantly higher risk, with a 4.6% risk per person-year compared to a 2.9% risk in those 75 or younger. 62.6% of those hemorrhages involved the gastrointestinal (GI) tract, and 18.1% of those admitted to the hospital for warfarin-related bleeds died within 7 days of discharge [38].

Due to such high mortality rates related to warfarin-associated bleeding, they are a large topic of discussion in the literature. ICH, particularly when related to traumatic injury, is a feared complications of anticoagulation use and has been associated with significantly higher mortality rates. For example, in one retrospective analysis warfarin use was found to be associated with a 6-fold increased mortality risk for ICH after blunt traumatic brain injury (TBI) compared to patients with TBI who were not on preinjury anticoagulation [39]. Another study investigating elderly patients with head injuries found that preinjury warfarin use both increased the ICH risk by 40% and doubled the risk of 30-day mortality compared to those not on warfarin [40].

One possible reason that could explain the high mortality rates seen in warfarin-associated ICH that has been supported in the literature may relate to the increased risk of hemorrhagic expansion in anticoagulated patients compared to non-anticoagulated patients. In a 2001 French study, researchers compared 3 groups of patients for analysis: those admitted due to anticoagulant-related ICH, a randomly selected group of patients admitted with spontaneous ICH, and those without ICH but who were on anticoagulation therapy. It was found that ICH

volumes in anticoagulated patients were significantly higher than those seen in spontaneous ICH based on CT scan measurements [41]. Another study conducted by Flibotte and colleagues at the Massachusetts General Hospital saw no effect of warfarin on initial ICH volume at presentation, but warfarin was found to be the only predictor of in-hospital hemorrhagic expansion. ICH expansion was then found to trend towards increased mortality, with warfarin patients overall being at significant risk for death, even after controlling for the initial ICH volume [42].

ICH is a significant adverse effect of anticoagulation therapy with severe effects on morbidity and mortality. Warfarin plays a considerable role in these outcomes, and the risk factors associated with adverse bleeding can be difficult to control, given that the major contributing risk factor, age, is non-modifiable. In acute situations where bleeding must be promptly addressed, reversal of anticoagulation is warranted. There are multiple pharmacological reversal agents that can counteract the antithrombotic mechanisms of warfarin and help prevent the sequelae of major bleeding. Prompt correction of coagulopathy associated with over-anticoagulation is recommended by current guidelines [43], and the following section aims to give a comprehensive discussion of important reversal agents that can achieve this.

Efficacy of Warfarin Reversal Agents

There are 3 pharmacological therapies available that can reverse the effects of warfarin: fresh frozen plasma (FFP), the prothrombin complex concentrates (PCCs), and phytonadione (vitamin K). Each agent has its own advantages and disadvantages, but the general consensus is that prompt reversal of warfarin in patients presenting with dangerous bleeds, such as an ICH, can contribute to decreased morbidity and mortality. Although a supratherapeutic INR is often implicated in increased bleeding risk, current guidelines suggest that for any patient presenting with a life-threatening bleed, prompt administration of reversal agents is warranted regardless of the presenting INR value [44]. In one study comparing times to reversal in anticoagulated traumatic ICH patients, patients in whom reversal therapy was initiated in under 2 hours as part of a rapid treatment protocol had both decreased rates of worsening ICH progression, as well as significantly lower mortality, than patients receiving reversal under an older protocol, in which it took more than 4 hours to initiate treatment [45]. Multiple guidelines, including those by the AHA/ASA [46] and the Neurocritical Care Society/Society of Critical Care Medicine [47], highly recommend immediate reversal in VKA patients presenting with ICH. The greatest source of debate within the literature in recent years, therefore, has not been whether reversal is warranted for warfarin-related hemorrhage, but instead involves the question of which of the 3 available reversal agents are most effective at both quickly counteracting the effects of the medication and improving overall outcomes in bleeding patients.

Full discussion of phytonadione will be limited in scope, primarily because it has little use as an agent for acute bleeding in emergency situations due to inappropriately long response times in reversing warfarin. In one randomized trial comparing omission of warfarin therapy to omission of warfarin therapy combined with oral phytonadione therapy, the mean time to achieve an INR ≤4 for over-anticoagulated patients presenting with an initial INR of 6 – 9 was 1.4 days. Although significantly faster than omission of warfarin therapy alone (which took 2.6 days in comparison) [48], this would be an inadequate treatment for a patient presenting with a more time-sensitive, warfarin-related coagulopathy, such as an ICH. Another disadvantage to vitamin K, especially if given at high doses, is that it can make patients refractory to future warfarin therapy when anticoagulation is eventually restarted [49]. Use of low doses of oral phytonadione as a monotherapy is therefore currently limited to patients who do not require urgent warfarin reversal [50].

Historically, FFP in combination with vitamin K had long been the standard of care in reversing the effects of over-anticoagulation [51] [52]. FFP can be prepared from either whole blood or plasma, and contains all of the clotting factors inhibited by warfarin and more, including fibrinogen, antithrombin and tissue factor pathway inhibitor. With appropriate dosing, FFP administration can increase the levels of deficient clotting factors by up to 30% [53], making it an effective therapy for warfarin reversal. In the United States, FFP is the most widely used coagulation factor replacement therapy [54], and this use has only been increasing over time. In

2008, 4.5 million units of FFP were transfused in the United States, compared to 3.9 million units in 2001 [55], for an average of now nearly 12,000 units used daily nationwide. One of the most common indications for FFP use is for warfarin reversal, as has been consistently cited in analyses conducted within both the United States [56] and abroad [57].

Despite its widespread use, administration of FFP is limited by several factors. Significant effort is required in preparing the infusions, FFP has a relatively slower therapeutic onset compared to other reversal alternatives (i.e. PCC), and there are many clinical adverse side effects associated its use. To adequately prepare a unit of FFP, the sample first undergoes type-specific matching, thawing, and delivery from the blood bank [54]. The thawing step can take anywhere from 30 – 60 minutes alone [58]. These steps can delay initiation of treatment, which is significant especially in time-sensitive situations. Even if prepared promptly, FFP has a rather slow therapeutic effect and can take 7 – 32 hours to achieve effective INR reversal in warfarin patients presenting with major hemorrhage [54], which is not ideal for life-threatening bleeding in which prompt reversal is required.

After transfusion, there are several serious adverse effects associated with FFP to be aware of. Of all blood products, FFP is the major cause of the life-threatening condition known as transfusion-related acute lung injury (TRALI). The underlying pathophysiology of TRALI is speculated to be related to an inappropriate immune response involving either donor antibodies, human leukocyte antigen (HLA) responses, and/or active recipient lung leukocytes that are

reacting to certain biological components of the donor's blood products. The endpoint of these aberrant immune responses is significant pulmonary endothelial damage [59]. Symptoms and clinical findings of TRALI include acute respiratory distress, non-cardiac pulmonary edema, bilateral infiltrates on chest x-ray, tachycardia, and hypoxemia within 6 hours of the transfusion. The absence of concomitant risk factors for the development of lung injury, such as sepsis, pneumonia, and shock, increase the clinical suspicion for TRALI in a recently transfused patient [60]. Statistically, transfusion of every 1 in 2,000 units of a plasma-containing blood component leads to an episode of TRALI, and fatality rates after diagnosis can range between 5 – 25% [61]. In one 5-year retrospective review study, FFP was associated with 50% of fatal TRALI cases, with red blood cells (RBCs), platelet products, and cryoprecipitate-reduced plasma responsible for the rest [59]. TRALI is overall the highest leading cause of transfusion-related morbidity and mortality in the United States [62], making it a serious clinical consequence of FFP use.

Another significant risk to FFP use is volume overload, otherwise known as transfusion-associated circulatory overload (TACO). FFP in particular is a major risk factor for developing TACO due to the high volumes of plasma required to achieve adequate therapeutic effects. The number of FFP units transfused has also been shown to strongly correlate with the subsequent development of fluid overload [62]. After TRALI, TACO is the second-leading cause of transfusion-related mortality in the United States. Rates of TACO following FFP administration varies,

with studies reporting values between 1.5 – 6%. Patients with TACO were found to have increased rates of in-hospital mortality, and both significantly longer hospital and intensive care unit (ICU) stays [63] [64].

FFP use is associated with other unique side effects. Since FFP is derived from donated human blood products, its administration can increase the risk of infectious disease transmission and immune reactions. These include viral, bacterial, parasitic, and prion diseases, febrile and allergic reactions, and ABO blood group incompatibility [65]. In a 2008 study, FFP transfusion in critically ill patients in an inpatient surgical ICU (SICU) was found to be significantly associated with higher rates of subsequent ventilator-associated pneumonias, bloodstream infections, and septic shock. The researchers attributed these increased risks to a transfusion-related phenomenon known as immunomodulation, which involves alterations in the systemic immune response due to transfusion of immunosuppressive proteins and/or disrupted white blood cell (WBC) products within the plasma [66]. These reactions, taken together with previously mentioned complications such as TRALI and TACO, are serious adverse effects that should be weighed with the benefits to FFP use prior to administration.

An alternative to FFP as a VKA-reversal therapy are the PCCs. PCC is a plasma-derived factor concentrate that was originally developed for the treatment of hemophilia B as a source of factor IX [67]. PCC contains variable amounts of the vitamin K-dependent coagulation factors II, VII, IX, and X, and can be further classified based on the quantity of factor VII present in the concentrate: 3-factor

PCC contains negligible amounts, while 4-factor PCC contains therapeutically restorative levels (for the remainder of this paper, any mentions of PCC will refer solely to the 4-factor preparation, unless otherwise specified).

The first successful documentation of PCC as an anticoagulation reversal therapy was in a 1976 randomized trial comparing 3-factor PCC to intravenous vitamin K therapy. The researchers found that PCC was associated with more rapid, albeit less sustained, reversal of both the prothrombin and partial thromboplastin times compared to vitamin K alone [68]. A 2007 comprehensive 30-year review of all prospective trials comparing PCC to other reversal agents, conducted prior to PCC's official approval as a reversal therapy by the FDA, found that PCC was associated with multiple clinical benefits, including more rapid INR correction, effective factor replacement, and decreased risks of thrombotic adverse events [52]. In 2013, PCC was officially approved by the FDA for the reversal of coagulopathy in over-anticoagulated patients [69], which is now the primary indication for its use. It is now rarely indicated as replacement therapy in patients with congenital factor deficiencies [70] – the original reason for its development – and has largely been replaced either by concentrates of individual clotting factors or recombinant factor products, especially following the introduction of these products in the 1990s [67] [71].

First, preparing PCC units for infusion is a significantly less intensive process relative to FFP. PCC does not require cross-matching, is stored at room temperature (and therefore does not require thawing), undergoes viral inactivation to reduce the

risk of infectious transmission, and can be completely infused in 15 – 30 minutes [72] [50]. These benefits are especially ideal for acute situations in which preparation time should be minimized. Additionally, TRALI, a feared complication of FFP use, is unlikely with PCC because the concentrates do not contain leukocytes that could trigger aberrant immune responses in donors [73]. PCC is also very unlikely to cause TACO because the units are freeze-dried to remove all water particles (e.g. lypophilized), and PCC can therefore be administered in smaller volumes [74]. For comparison, FFP is typically administered at a dose of 15 mL/kg, while an equivalent PCC dose can be given at a volume of 1-2 mL/kg [74]. In one randomized control trial comparing the two reversal modalities for patients presenting with VKA-associated coagulopathy, the median infusion volumes needed to achieve therapeutic effect for PCC and FFP were 99.4 and 813.5 mL, respectively [75].

However, PCC is not without its own set of adverse side effects. As with any transfusion of blood products, anaphylactic reactions have been associated with PCC administration, and since most PCC preparations contain heparin, heparin-induced thrombocytopenia (HIT) has been documented as well. Although PCC is pretreated to inactivate most viral pathogens, contamination of the products with non-enveloped viruses has occurred. Thrombogenic complications including stroke, MI, disseminated intravascular coagulation (DIC), and DVT have also all been attributed to PCC use [70] [74], albeit that composite risk remains low at 1.4%, according to a recent literature review [52]. Since most of these adverse effects are quite rare, PCC is overall a safe and effective therapy for warfarin reversal.

Armed now with a better understanding of the primary agents available for VKA reversal, the next important question to consider is whether there is a superior reversal therapy that is associated with the best clinical outcomes in situations requiring reversal of anticoagulation in patients presenting with severe bleeding, especially ICH. In the upcoming section, we conduct a brief literature review of the clinical studies that directly compare PCC to FFP for urgent reversal, with a primary focus on life-threatening ICH associated with anticoagulation therapy.

PCC vs. FFP: A Superior Agent?

Current guidelines have now shifted their recommendations to PCC for the urgent reversal of VKAs in life-threatening warfarin-related bleeds [76], given that PCC has been shown repeatedly in numerous clinical trials and reviews to have many advantages over FFP. One of the earliest such reports that aimed to directly compare the 2 reversal therapies for this purpose was a 1997 prospective investigation by Makris and colleagues conducted in the United Kingdom, in which patients requiring urgent reversal of their oral anticoagulation therapy received either FFP or PCC. PCC use was associated with complete INR correction in all patients and greater restoration of hemostatically effective levels of clotting factors (especially factor IX), whereas in contrast, the INR failed to correct adequately in all patients receiving FFP. Nearly 2 decades before the FDA would officially approve PCC as a reversal agent for severe, anticoagulation-associated bleeding, the authors

of this study strongly concluded that PCC is the only effective option for correcting coagulopathies in patients with life-threatening hemorrhage [77].

Several systematic analyses of studies comparing reversal agents in patients requiring urgent warfarin reversal also have found benefits to PCC use. One meta-analysis of 13 relevant studies found that PCC use was associated with a lower risk of all-cause mortality, higher proportion of hemostasis, greater and more rapid INR normalization, and lower risk of post-transfusion volume overload compared to FFP [78]. Another 2017 analysis by Harrison et al. found that PCC was associated with a 3.65% risk reduction in 30-day mortality relative to FFP [79].

Benefits to PCC were also seen in the results of several randomized controlled trials, some of which were included for review in the meta-analyses discussed above. In one prospective trial conducted across numerous sites in both the United States and Europe, VKA patients presenting with both acute major bleeding and elevated INR ≥2.0 were randomized to receive either FFP or PCC for urgent reversal. PCC use was found to be associated with more rapid INR reduction (defined as an INR ≤1.3 half an hour after infusion) and higher levels of plasma coagulation factors relative to FFP [75]. In a similar randomized trial by Goldstein et al., patients received vitamin K with either concomitant PCC or FFP therapy for rapid VKA reversal. PCC was found to be superior to FFP in achieving both effective hemostasis and rapid INR reduction [80]. In both of these trials, rates of adverse events such as thromboembolism, fluid overload, late bleeding, and death, were similar between treatment groups.

Those results were later confirmed in a more recent 2016 randomized trial conducted in Germany. This study was unique in that it was the first randomized trial to compare reversal therapies in patients specifically presenting with VKA-related ICH, especially since the previous 2 randomized trials comparing PCC to FFP had few patients with this specific bleeding complication in the study cohorts (for example, only 2 of the 181 bleeding patients in the Goldstein study required a neurosurgical procedure). In the German study, only 9% of FFP patients achieved the primary endpoint of an INR ≤1.2 within 3 hours of treatment initiation, as opposed to 67% of PCC patients. All deaths associated with hematoma expansion were in the FFP group, again suggesting inadequate hemostasis in patients receiving FFP as opposed to PCC [81].

While the German study is the only randomized trial to compare reversal for warfarin-related ICH, the researchers excluded trauma-related ICH. However, evidence for PCC's benefits in clinical scenarios specifically involving traumatic ICH has also been seen in other observational and retrospective studies. In a 2013 study of patients presenting with an ICH requiring urgent reversal, PCC achieved significantly faster INR reversal than FFP [82]. A similar 2014 observational study likewise found that PCC was associated with a faster time to INR reversal, as well as a significantly shorter delay in the time to neurosurgical intervention [83]. Use of PCC also has been shown to decrease the incidence of ICH progression in patients presenting with traumatic, warfarin-related bleeds [84].

The literature clearly supports the use of PCC for urgent reversal in life-threatening bleeds. However, one area that has received relatively less attention is the comparison of reversal agents for ICH specifically in patients of advanced age. This is a particularly important population to consider given that patients over 65 years of age are more likely to be on an anticoagulative medication such as warfarin, advanced age is one of the strongest independent risk factors for anticoagulative-related bleeding, and the second leading cause of injury after motor vehicle crashes in this population are falls, which can further increase the risk of bleeding. Trauma-related ICH in an elderly patient on anticoagulation is a substantial risk that can have devastating consequences. In fact, preinjury warfarin use in elderly brain injured patients has been associated with far worse outcomes relative to those seen in their younger counterparts.

In one retrospective analysis of elderly TBI patients, oral anticoagulation with warfarin was significantly associated with increased mortality, need for neurosurgical intervention, and risk of in-hospital death. These risks were not associated with the use of preinjury antiplatelet medications, such as aspirin or clopidogrel [85]. In older patients, an INR as low as 2 has been associated with increased severity of TBIs, overall mortality, risks of ICH, and risks of subsequent ICH-associated mortality (in contrast, recall that the therapeutic INR range for warfarin patients ranges between 2.0 – 3.5) [86]. In one retrospective analysis of patients 55 years or older presenting with TBI, use of oral anticoagulation and antiplatelets was related to more in-hospital mortality, progression of the bleed,

development of new hemorrhagic foci, and discharge to a care facility compared to patients not taking those preinjury medications [87].

With the projected elderly population age 65 years and older expected to reach 52 million by the year 2020 [88], understanding the indications, benefits, risks, and the most effective methods for warfarin reversal are crucial to ensure the best outcomes in this vulnerable population.

Statement of Purpose

This retrospective study aims to identify differences in clinical outcomes, costs, and trends associated with the use of FFP, PCC, or no reversal agent in patients 65 years old and older with a traumatic ICH on preinjury warfarin presenting to our academic level 1 trauma center. Our study is unique from prior studies in that we also consider in our comparison the absence of the use of a reversal agent. We hypothesize that the use of PCC will result in improved clinical outcomes compared to either FFP or no reversal agent.

Methods

Data & Study Sample

After obtaining approval from the Yale Human Investigations Committee, we retrospectively reviewed all patients 65 years of age or older on preinjury warfarin diagnosed with traumatic ICH admitted to Yale New Haven Hospital, an academic Level 1 trauma center from January 2013 through December 2018 (n=190) via the internal electronic medical record (EMR) system. The ICH types included were: subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), epidural hemorrhage (EPH), and/or intraparenchymal hemorrhage (IPH) identified through the trauma registry. Patients who were admitted for comfort measures only (n=18), were deemed to have a non-survivable injury (n=3), had no follow-up head CT scan (n=12), or received both FFP and PCC as part of their treatment (n=8) were excluded from analysis. This yielded a final sample of 150 patients.

Follow-up CT scans were obtained at 6 hours after the initial CT scan. The study sample was then stratified based on the type of reversal agent used: PCC, FFP, or no reversal agent. Data on baseline demographics (sex, race), mechanism of injury, admission INR, Injury Severity Score (ISS), head Abbreviated Injury Score (AIS), Glasgow Coma Scale (GCS) score, whether the patient was transferred from an outside hospital (OSH), comorbidities (hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD)), use of vitamin K therapy and preinjury use of concomitant antiplatelet drugs were also recorded.

Outcomes

The 3 primary outcomes were ICH progression on follow-up CT scan, need for craniotomy, and in-hospital mortality. We chose to include ICH progression as one of our primary outcomes because we believe it to be a more sensitive indicator of the efficacy of reversal agent. ICH progression was defined as a radiology report that indicated increasing size and/or expansion of a head bleed on follow-up CT scan relative to the initial CT scan obtained on admission. Secondary outcomes included hospital length of stay (LOS), admission to the intensive care unit (ICU), ICU LOS, need for mechanical ventilation, total days spent on mechanical ventilation, change in neurologic exam, and number of hours until the INR decreased to a value of <1.2. The costs associated with the use of reversal agent per patient were calculated by averaging the number of units of either FFP or PCC given, and using available institutional labor cost data, cost per unit of FFP and the average wholesale price (AWP) of PCC, respectively, to determine the expenses.

Statistical Analysis

All statistical analysis was performed using SAS version 9.4 (Carry, NC). The Chi-square test was used to compare categorical variables, and the independent *t*-test was used to compare normally distributed variables. Variables with non-normal distributions were compared using the Kruskal-Wallis test. Bonferroni corrections were used to adjust for multiple comparisons. Logistic regression was

used to assess for differences in outcomes with models adjusted for demographics, admission INR, use of vitamin K, concomitant antiplatelet therapy, head AIS score, and GCS score. Use of any antiplatelet medications were grouped together into one variable given the few patients on medications other than aspirin. Lastly, the Cochran-Armitage test was used to assess for trends in the use of the various agents over time. All statistical analysis was performed by Dr. Kevin Schuster, Associate Professor of Surgery (Trauma) in the Yale Medicine section of General Surgery, Trauma, and Surgical Critical Care.

Results

Of 150 eligible patients with complete data, 41 patients received FFP (27.3%), 60 received PCC (40%), and 49 (32.7%) were not reversed. There were no significant differences between groups with regards to age, sex, race, mechanism of injury, type of ICH, ISS, AIS, GCS, and concomitant use of antiplatelet therapy (Table 1). Among all three groups, admission INR was highest in the group that received FFP (2.94) and lowest in the group not reversed (2.02, $p = 0.006$), but was not statistically significant when comparing INR values for PCC and FFP groups ($p = 0.592$). There was no difference between groups for the comorbidities diabetes (DM) ($p = 0.983$) or coronary artery disease (CAD) ($p = 0.094$), but patients who received PCC were more likely to have hypertension (88%) ($p = 0.021$) compared to those who received FFP (71%) or no agents (67%). Finally, patients who received PCC were more likely to have received vitamin K (90%) than any other patient group ($p < 0.001$).

		PCC (n=60)	FFP (n=41)	No Reversal (n=49)	p-value
Age (mean, SD)		81.9 (8.1)	81.2 (9.7)	81.3 (7.3)	0.889
Male (n, %)		35 (58.3)	18 (43.9)	24 (49)	0.334
Race (n, %)					0.951
	White	50 (83)	34 (83)	44 (90)	
	Black	4 (7)	3 (7)	3 (6)	
	Other	6 (10)	4 (10)	2 (4)	
Mechanism of injury (n, %)					0.248
	Fall	59 (98)	38 (93)	48 (98)	
	Other	1 (2)	3 (7)	1 (2)	
ICH Type (n, %)					0.566
	SAH	29 (48.3)	23 (56.1)	32 (65.3)	0.207
	SDH	38 (63.3)	28 (68.3)	25 (51)	0.868
	EPH	2 (0.033)	1 (0.024)	0 (0)	0.453
	IPH	5 (0.083)	2 (0.049)	5 (10.2)	0.646

Admission INR (mean, SD)		2.77 (1.3)	2.94 (1.9)	2.02 (1.4)	0.006
ISS (mean, SD)		15.8 (8.5)	15.2 (8.0)	13.6 (7.4)	0.341
AIS head (median, IQR)		2 (1, 3)	1 (1, 2)	2 (1, 3)	0.864
GCS (mean, SD)		14.4 (1.7)	14.05 (2.4)	13.96 (2.6)	0.441
Transfer from OSH (n, %)		14 (23.3)	14 (34.1)	11 (22.4)	0.376
Comorbidities (n, %)					0.767
	HTN	53 (88)	29 (71)	33 (67)	0.021*
	DM	17 (28)	11 (27)	14 (29)	0.983
	CAD	22 (37)	11 (27)	24 (49)	0.094
Concomitant antiplatelet therapy (n, %)		16 (26.7)	12 (29.3)	21 (42.9)	0.173
Administered Vitamin K (n, %)		54 (90)	33 (80.4)	16 (32.7)	<0.001*

Table 1: Demographic information of patients who received PCC, FFP, and no reversal agent. 4-factor prothrombin concentrate (PCC), fresh frozen plasma (FFP), subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), epidural hemorrhage (EPH), intraparenchymal hemorrhage (IPH), International Normalized Ratio (INR), Injury Severity Score (ISS), Abbreviated Injury Score (AIS), outside hospital (OSH), hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), standard deviation (SD), interquartile range (IQR).

Of all patients, 38% (n=57) experienced progression of their bleed according to follow-up CT scans. On bivariate analysis, patients who received FFP were more likely to have had ICH progression (51.2%) compared to those who received PCC (43.3%) or no reversal agent (20.4%) (p = 0.006). There was no difference in the rates of mortality or the need for surgical intervention between the three groups (Table 2).

For secondary outcomes, FFP patients had longer hospital LOS, spent more time in the ICU of those admitted to the ICU, and more often required mechanical ventilation. Time to reversal was most rapid in the PCC group (median 10.5 hours, IQR 6-17.5 vs. 21 hours, IQR 15-36 in FFP group, p = 0.002). There was no significant

difference between groups in ICU admissions, total number of days spent on mechanical ventilation, or worsening mental status (Table 2).

	PCC (n=60)	FFP (n=41)	No Reversal (n=49)	p-value
ICH Progression (n, %)	26 (43.3)	21 (51.2)	10 (20.4)	0.006*
Need for craniotomy (n %)	9 (15)	8 (19.5)	3 (6.1)	0.157
Mortality (n, %)	2 (3.3)	0 (0)	2 (4.1)	0.448
LOS (days, median, IQR)	4 (3-7)	6 (3-13)	4 (2-5)	0.024*
ICU Admit (n, %)	34 (56.7)	23 (56.1)	19 (38.8)	0.128
ICU LOS (median, IQR)	7 (3, 18)	7 (4, 13)	4 (2, 15)	0.422
Mechanical ventilation (n, %)	4 (6.7)	9 (22)	4 (8.2)	0.041*
Vent Days (median, IQR)	0 (0, 0)	1 (0, 4)	0 (0, 0)	<0.001*
Worsening mental status (n, %)	18 (30)	13 (31.7)	11 (22.4)	0.563
Time to INR <1.2 (hours, median, IQR)	10.5 (6, 17.5)	21 (15, 36)	N/A	0.002*

Table 2: Primary and secondary outcomes of patients who received PCC, FFP, and no reversal agent. Length of stay (LOS), intensive care unit (ICU).

On multivariable analysis, no reversal and female gender were associated with a decreased likelihood of ICH progression on follow-up CT scan, while the presence of SDH was associated with progression of the bleed (Table 3). Admission INR, co-administration of vitamin K, and use of concomitant antiplatelet therapy were not associated with ICH progression. Multivariable analysis of mortality demonstrated only higher presenting GCS (OR 0.75, 95% CI [0.60 – 0.95]) as protective. The absence of reversal (OR 0.78, 95% CI [0.07 – 8.96]) and use of FFP (OR 0.42, 95% CI [0.04 – 4.44]) compared to PCC did not impact mortality. Multivariable analysis of the need for craniotomy demonstrated no effect for not reversing (OR 0.29, 95% CI [0.03 – 2.56]) or use of FFP (OR 2.51, 95% CI [0.64 – 9.93]).

Patient Characteristic	Odds Ratio (OR)	95% CI	P Value
IPH	1.35	0.31 – 5.98	0.689
SAH	2.06	0.74 – 5.74	0.165
SDH	3.69	1.27 – 10.73	0.017*
EDH	0.57	0.01 – 38.98	0.794
PCC	*Reference*		
No Reversal Agent Used	0.25	0.31 – 0.85	0.010*
FFP	1.13	0.44 – 2.90	0.070
Female	0.38	0.17 – 0.88	0.023*
Admission INR	1.01	0.79 – 1.30	0.923
Administered Vitamin K	2.13	0.73 – 6.24	0.168
Concomitant Antiplatelet Therapy	1.56	0.63 – 3.86	0.331
Head AIS - 1	1.25	0.34 – 4.64	0.031*
Head AIS – 2	0.54	0.13 – 3.11	0.870
Head AIS – 3	0.57	0.02 – 1.39	0.970
Head AIS – 4	0.17	0.02 – 1.39	0.100
Head AIS - 5	*Reference*		
GCS	0.84	0.70 – 1.00	0.050

Table 3: Multivariable analysis of predictors of ICH progression on follow-up CT scan.

Throughout the study period, the usage of reversal agent by year also significantly shifted (Table 4, Figure 1). Use of FFP decreased from 68% in 2013 to 3% in 2018, and use of PCC increased from 0% in 2013 to 76% by 2018 ($p < 0.001$). The proportion of patients receiving no reversal also decreased from approximately 30% to a low of 21% in 2018 ($p < 0.001$).

Cost calculations were based on 41 patients who received FFP at an average of 3.54 units per person. FFP costs at our institution are 35 USD per unit, with an additional 16.25 USD cost associated for lab labor, bringing the total cost per unit of FFP to 51.25 USD. Therefore, the average cost per patient to administer FFP was approximately 181 USD. Sixty patients received PCC at an average of 1,725 units

per person. At an AWP of 2.90 USD per unit, the average cost to administer PCC per patient was 5,003 USD.

Reversal Agent	2013	2014	2015	2016	2017	2018
No Reversal Agent	32	38	30	52	29	21
FFP	68	29	35	19	13	3
PCC	0	33	35	29	58	76

Table 4: Therapy used (no reversal agent, FFP, or PCC) in % over time.

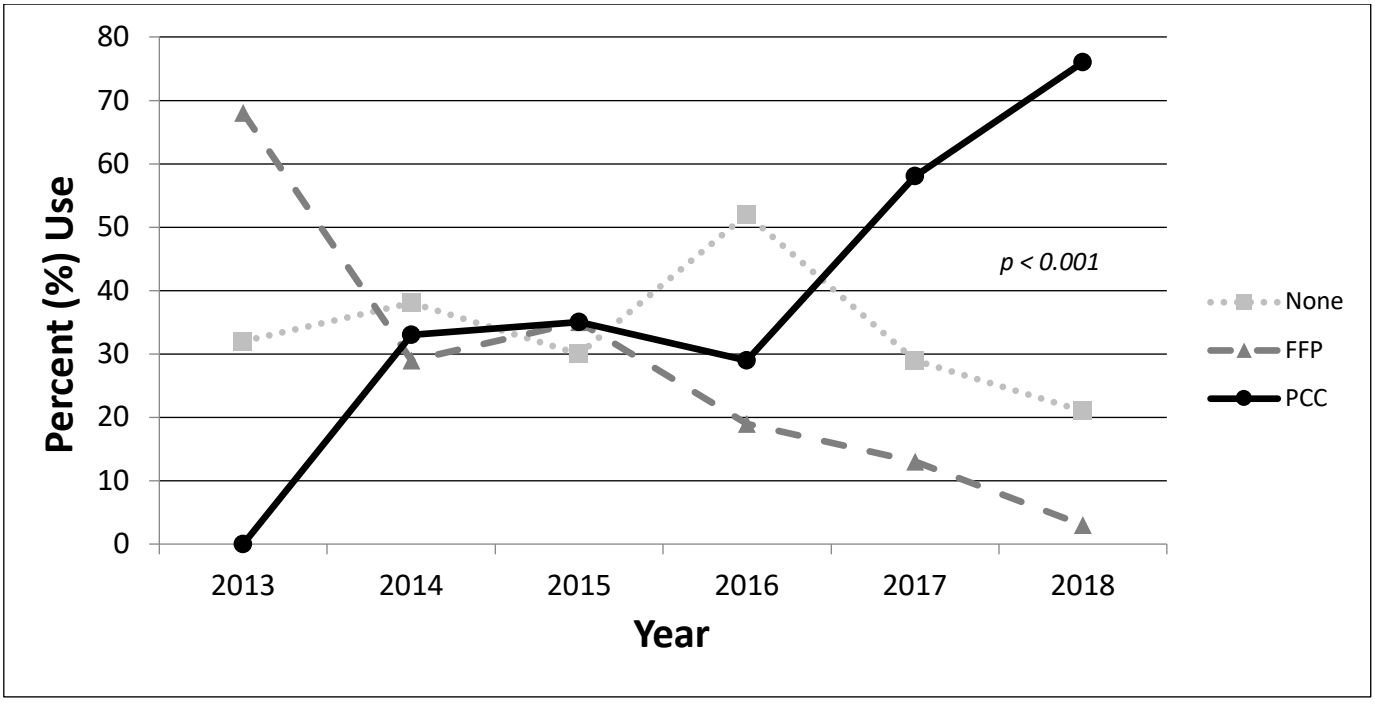

Figure 1: Therapy used (no reversal agent, FFP, or PCC) in % over time.

Discussion

While there are many studies that have compared outcomes between the use of PCC versus FFP for warfarin reversal in head trauma patients, they have not included patients observed without reversal. This study is significant in that it demonstrates an association between lower rates of hemorrhagic progression in older patients who are not reversed, in contrast to our original proposed hypothesis. Equivalently, patients who did receive reversal agents were paradoxically more likely to experience bleed progression, especially in the subset of patients receiving FFP. This was similarly observed in the prospective, observational Frontera et al. study, which compared outcomes in patients presenting with warfarin-related ICH who received either PCC, FFP, or PCC and FFP. The authors found that using FFP alone for warfarin reversal was significantly associated with greater rates of major hemorrhage, defined as new or worsening ICH, anemia requiring transfusion, or GI bleed, after administration than with PCC [89]. However, our study was different in that we examined a third group of ICH patients that underwent no warfarin reversal.

This finding is important because we concomitantly observed that the proportion of patients receiving no reversal in our institution overall decreased since the introduction of PCC. We speculate that this is indicative of a lower clinical threshold for clinicians to provide warfarin reversal when a drug, i.e. PCC, with presumed fewer side effects than the prior standard of care is readily available. Therefore, improvements in patient outcomes when retrospectively comparing PCC

to FFP, as was seen in a large proportion of the prior literature, are likely partially artifact in both our study and in others that only compared those two treatment groups, and did not consider this third group of patients who received no reversal agent. Patients once deemed to be at low risk for bleed progression are now likely being included in higher numbers in the PCC treatment groups, even though these patients would likely not have been reversed at all prior to the FDA approval of PCC. Because the group with no reversal also had comparatively better outcomes, without differences in baseline GCS, head AIS, or other clinical variables likely associated with the decision to reverse, we believe clinicians use other subjective parameters to effectively identify patients who are likely to do well without pharmacological reversal. Also implied in these findings is the likelihood that many patients who were reversed, especially with FFP, ultimately did not benefit from reversal. Although the risk is likely low, these patients could have experienced the potential for harm due to thromboembolic events or other medication side effects and there was increased cost.

Similar to prior studies, PCC therapy was associated with more rapid correction of the INR relative to FFP. It also correlated to shorter hospital stays and fewer requirements for mechanical ventilation. This is despite the fact that in this study population, there were no differences in severity of the initial injury. The improvements in outcome measures between the two treatments may therefore be related to the smaller fluid loads associated with PCC administration relative to that

of FFP, an advantage to PCC use that we explored in-depth in the introduction section.

Additionally, although initial INR values were statistically similar when comparing the PCC and FFP patients and were highest in reversed patients, INR was ultimately not found to be associated with an increased likelihood of bleed progression on multivariable analysis. This further strengthens the inference that reversal based solely on presenting INR may ultimately not be beneficial to a substantial number of patients presenting with traumatic ICH. This lack of association between INR and severity of bleeding has likewise been seen in prior studies. In a 2005 study investigating rapid warfarin reversal in patients presenting with ICH, it was found that neither the initial GCS nor INR value in these patients were able to reliably identify patients with an ICH. Patients presenting with an ICH had a median INR of 2.7, compared to 2.5 in patients without an ICH, a difference that was statistically insignificant [45]. Although all patients in our study population presented with an ICH and we specifically were comparing rates of hemorrhagic expansion, we likewise found that there was no significant difference in the presenting INR value in patients requiring reversal, yet did see subsequently significant differences in bleed progression.

Unlike many of the outcomes seen in prior studies, we found no significant difference in mortality between patients who received either of the two reversal agents or no reversal. Use of a reversal agent also had no relationship with the need for surgical intervention. In a study similar to ours, Zubkov and colleagues

demonstrated that INR at presentation was not associated with adverse outcomes, while other clinical findings, including presenting level of consciousness and initial ICH volume, were significant predictors of worse prognosis in patients presenting with an ICH on preinjury warfarin [90]. Going forward, it will therefore be important to understand the clinical rationale behind choosing to reverse an anticoagulated patient presenting with a traumatic ICH. Because injury severity was essentially similar between our treatment groups, there may have been unknown subjective factors that could better explain why physicians chose to initiate reversal, ones that perhaps had no influence on either mortality or the need for surgical treatment. These factors may have played a role in the decision to reverse, as well as the subsequent outcomes, in complex ways not identifiable in a retrospective study.

Another unique aspect of our study is that we compared trends in the use of reversal agents over time. Throughout our study period, use of the reversal agent PCC increased significantly from 0% in 2013, which was prior to availability at our institution, to 78% in 2018. This increase in use was then associated with a 27-fold increase in costs to reverse a patient requiring treatment. PCC's perceived advantages and improved availability relative to FFP likely prompted this change in practice. However, this cost is likely offset to some degree by the costs of the increased mechanical ventilation requirements and longer hospital stays experienced by the FFP group. To date, our study is the first in its kind to additionally compare these aspects of care, and follow-up investigations could expand this data on a national scale.

There are several limitations to our study. The most important aspect is its retrospective nature, which introduces potential selection bias. We are unable to discern whether a patient was reversed specifically to address either the presenting INR, radiological findings on CT scan, physical examination findings, symptomatology, or a combination of all of these. Physicians may have also chosen treatment based on unmeasured patient characteristics for which we cannot fully control and that may therefore not have been accurately reflected or recorded in the EMR, making data collection of these characteristics difficult. We did mitigate against this by controlling for all of the factors that were measurable and might impact a clinician's decision to choose one method of reversal or no reversal. We were also limited by our choice of outcome. Though clinical deterioration, need for surgery and mortality are all impactful outcomes, our limited number of patients and therefore, our limited statistical power, may have prevented us from demonstrating outcome differences based on these measures. We do believe, however, that bleed progression is a likely surrogate for these more important outcomes if the study population is sufficiently large.

Additionally, although the time to repeat CT scan is standardized at our institution, there was some variation in the timing that was beyond our control, and a few patients could not be included in our study because no repeat CT scan performed in a timely fashion. Although the use of follow-up CT scans is controversial, they may demonstrate outcome differences that would otherwise become evident if larger numbers of patients were studied. We chose this outcome,

therefore, as an intermediate marker. Similarly, the timing of repeat coagulation testing was not standardized at our institution, though prior studies have demonstrated similar decreased times to normalization of the pharmacologic coagulopathy. We were also limited in assessing overall charges based on institutional policy, and can only provide cost data for the reversal agents themselves. Lastly, all data analyzed were taken from one single academic institution, and cannot necessarily be extrapolated to other centers. This limitation will hopefully be addressed in a multi-institutional study to measure the impact of FFP, PCC or no reversal in a larger series.

In conclusion, we have demonstrated that reversal of warfarin may not be beneficial in select patients. Although PCC provides for relatively effective and rapid reduction in INR, as was seen both in our study and in prior literature, the choice to reverse the coagulopathy ultimately did not affect mortality or the need for neurosurgical intervention. Over time, the use of the readily available PCC, with its improved side effect profile over FFP, was rapidly adopted, and likely led to the increased treatment of patients with PCC that would have been equally served with no treatment. This has significant effects on costs of therapy, as PCC was found in our institution to be significantly higher than those associated with FFP use. Moving forward, we should continue to further define those populations that may not benefit from, and might even be potentially harmed, by warfarin reversal in order to improve patient outcomes and reduce costs.

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