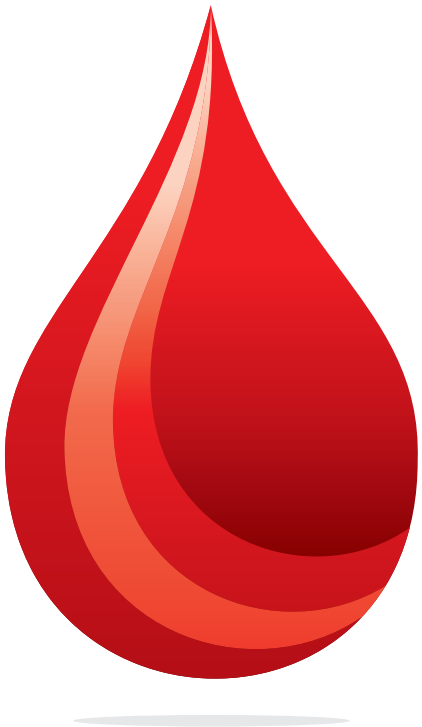
Review Article



Literature Review of Fixed and Weight-Based Dosing of 4-Factor Prothrombin Complex Concentrate in Achievement of Hemostasis in Adult Patients Taking Factor Xa Direct Oral Anticoagulants

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Clinical Question

How does fixed dosing of 4-factor prothrombin complex concentrate (4F-PCC) compare to traditional weight-based dosing of 4F-PCC in achieving hemostasis in adult patients taking factor Xa direct oral anticoagulants (DOACs)?

Major bleeding is an unfortunate risk of anticoagulation therapy. Currently, andexanet alfa is the only approved agent for reversal of factor Xa DOACs.[1] Other agents, including 4F-PCC, have been used off-label for the reversal of DOACs in the setting of major bleeding. Factor Xa DOACs, which include rivaroxaban, apixaban, edoxaban, and betrixaban, target Xa to block the coagulation cascade. 4F-PCC can be used as a reversal agent because it contains coagulation factors II, VII, IX, and X, as well as proteins C and S.[2] An additional benefit to using 4F-PCC over other approved reversal agents is a significant cost savings. Wilsey et al. calculated the cost of a dose of andexanet alfa to be $58,080, a 50 unit/kg dose of 4F-PCC to be $6,885, and a 25 unit/kg dose of 4F-PCC to be $3,443 for an 85-kg patient.[3]

In recent years, use of 4F-PCC for factor Xa DOAC reversal has become more common. Gundersen Health System in La Crosse, Wisconsin has a pharmacist-driven protocol to use 4F-PCC for reversal of warfarin, but still requires provider oversight for use in patients on DOACs. There is some discrepancy among some services, with some using fixed dosing of 2000 units and some using weight-based dosing of 50 units/kg. This literature review aims to provide data for pharmacists to use when providing recommendations for use of 4F-PCC for factor Xa DOAC reversal.

Literature Review

A 2020 single-center, retrospective cohort study evaluated achievement of hemostasis with fixed dosing versus weight-based dosing of 4F-PCC in patients taking direct factor Xa inhibitor oral anticoagulants.[4] Adult patients who were taking factor Xa inhibitor oral anticoagulation and received 4F-PCC from January 1, 2014 through December 31, 2018 at a 433-bed tertiary care hospital in central Kentucky were included in the study. This study included 72 patients, 46 of whom were taking factor Xa DOACs. The intervention was 4F-PCC, dosed at 35 units/kg for moderate bleeding, 50 units/kg for severe bleeding, or a fixed dose of 2000 units. The primary outcome was clinically effective hemostasis. In patients taking factor Xa DOACs, clinically effective hemostasis was achieved in 95% of patients who received fixed dosing and 76.9% of patients who received weight-based dosing (p=0.091). One limitation was the exclusion of patients who died within 24 hours of hospitalization. This may have impacted the results of this study, since the cause of death and treatment course were unknown.

A 2021 updated systematic review and meta-analysis evaluated the efficacy and safety of the use of 4F-PCC as a reversal agent in patients experiencing major bleeding who take factor Xa inhibitors.[5] Randomized controlled trials (RCT), prospective or retrospective cohort studies,

case control, and case series studies were included if they studied adult patients taking factor Xa inhibitors who received 4F-PCC for treatment of major bleeding. Trial bias was evaluated using the Joanna Briggs Institute critical appraisal checklist and low-quality studies were removed. A total of 33 studies (n=2568 patients) were included in the systematic review, and 29 in the meta-analysis. Of note, all studies were retrospective or prospective cohort studies.

The meta-analysis showed pooled proportion outcomes for hemostasis (80%, CI 0.75-0.84), mortality (15%, CI 0.11-0.19), and thromboembolic adverse events (3%, CI 0.02-0.05).[5] No difference was seen between high (>30 unit/kg/dose) (77%, CI 0.72-0.82) or low (<30 unit/kg/dose) (79%, CI 0.71-0.85) 4F-PCC in the efficacy of hemostasis. Publication bias was analyzed with funnel plots and the Egger's test. No publication bias was detected for thrombosis and hemostasis outcomes, but the Egger's test was positive for the mortality outcome. Moderate heterogeneity was detected between the studies (I^2 = 61%, p<0.01) and a sensitivity analysis to exclude outliers was performed. Presentation of dosing for each included study is a limitation of this analysis. Specific dosing was not reported for several studies, and upon further review, the study by Schulman et al. was reported as weight-based, but fixed dosing was actually used.[5,6] Another significant limitation is the possibility of confounders, since other hemostatic agents were likely given to these patients, but are not reported in this analysis.[5]

Given limited head-to-head data, a supplemental indirect comparison was included (Table 1). Attention was given to present comparable direct oral anticoagulants in the comparison.

Due to the nature of this topic, there are several limitations in the studies included in Table 1.[3,6,7] Notably, these studies all are small and underpowered. Schulman et al. had 12 patients who deviated from the fixed dosing protocol, and these patients are included in the overall efficacy data without differentiation, potentially leading to inaccurate results on hemostasis data.[6] Wilsey et al. had patients in both dosing groups who received packed red blood cells, platelets, and fresh frozen plasma along with or after their 4F-PCC.[3] The percentage of patients who received packed red blood cells in the low dose group was 8.4% higher than the high dose group and the percentage of patients who received fresh frozen plasma was 6.2% higher in the high dose group compared to the low dose group. These other agents may have affected the primary outcome of hemostasis. The study done by Majeed et al. had 3 patients who received a second dose of 500-1500 units of 4F-PCC due to inefficacy after the first dose.[7] The dose that these patients initially received is not reported, and these patients are included in the efficacy data. In a study of this size, these patients may make a difference in overall results.

Recommendations from Others

The American College of Cardiology published a 2020 expert consensus decision pathway (ECDP) to guide practitioners in management of bleeding in patients taking oral anticoagulants.[10] This consensus pathway is an update to their original ECDP that was published in 2017, and is derived from current scientific evidence and expert opinion. There is no grading system used in their summary. Regarding the use of prothrombin complex concentrate (PCC) in

TABLE 1. Effect of Weight-Based and Fixed Dosing of 4F-PCC in Patients Taking DOACs on Achievement of Hemostasis

Reference	Design	Inclusion Criteria	Number of Patients	Intervention	Results
Schulman et al (2018)[6]	Prospective, observational, multicenter, cohort study at a Canadian hospital, July 2014 – July 2017	Patients who received 4F-PCC and were taking rivaroxaban or apixaban and did not receive other hemostatic agents	N = 66 • 2000 units = 54 • 1000 units = 2 • 1500 units = 3 • 2500 units = 1 • 3000 units = 4 • 3500 units = 1 • 4200 units = 1	Fixed dose of 4F-PCC 2,000 units • Beriplex (10%) • Octaplex (90%)	Achievement of clinically effective hemostasis: • Good: 43 (65%; 95% CI, 53-77) • Moderate: 13 (20%; 95% CI 10-30) • Poor/none: 10 (15%; 95% CI, 6-24)
Wilsey et al (2021)[3]	Retrospective cohort study at a University of Kentucky level 1 trauma and stroke center, January 2015 – December 2018	Patients who experienced major bleeding and were taking apixaban or rivaroxaban and received 4F-PCC	N = 99 • Low dose: N=57 (57.6%) • High dose: N=42 (42.4%)	4F-PCC (Kcentra) • Low dose (20-34 units/kg) (mean dose = 26.6 units/kg) • High dose (35-50 units/kg) (mean dose = 47.6 units/kg) • Dosed using actual body weight with a dose cap at 100 kg	Oral Comparison of hemostasis between high and low doses of 4F-PCC: • 75.4% (low dose) • 78.6% (high dose) • p=0.715
Majeed et al (2017)[7]	Prospective cohort study using cases from 25 hospitals in Sweden, January 1, 2014 – October 1, 2016	Patients who had taken a dose of rivaroxaban or apixaban within 24 hours and received 4F-PCC due to acute and active major bleeding	N = 84	4F-PCC (Octaplex or Confidex/ Beriplex) given at a median, interquartile dose of 1500 – 2000 units with an approximate dose of 25 IU/kg • < 65 kg = 1500 units • > 65 kg = 2000 units	Achievement of clinically effective hemostasis: • Effective: 58 (69.1%) • Ineffective: 26 (30.9%) • No p value provided by authors

4F-PCC = 4-factor prothrombin complex concentrate

the management of bleeding in patients taking direct factor Xa inhibitor oral anticoagulants, they recommend using PCC if andexanet alfa is not available, and do not recommend a particular dose of PCC. They do recognize that evidence in this area is limited and 4F-PCC is the most studied to date.

The Anticoagulation Forum, which is made up of anticoagulation providers in North America, published guidance in 2019 on the reversal of DOACs.[11] This guidance is based on the best available evidence and expert opinion. There is no grading system used in their executive summary. Regarding use of PCC in the management of bleeding in patients taking direct oral anticoagulants, they have separate suggestions depending on specific DOAC. In rivaroxaban or apixaban treated patients, they suggest using 2000 units of 4F-PCC if andexanet alfa is not available. In edoxaban or betrixaban treated patients, they suggest using either high dose andexanet alfa or 2000 units of 4F-PCC.

Evidence-Based Answer and Strength of Recommendation (SOR) & Rationale

Fixed dosing of 4F-PCC may be comparable to traditional weight-based dosing of 4F-PCC in adult patients taking factor Xa DOACs in regard to hemostasis. (Strength of recommendation = B based on a single head-to-head cohort study and 3 well-done cohort studies looking at a patient-oriented outcome). Results from the included studies[3-7] share two common conclusions; 4F-PCC is effective in achieving hemostasis in patients taking factor Xa DOACs, but larger studies with head-to-head comparisons are needed to determine the optimal dose. As Wilsey et al pointed out, cost should also be considered, as there is approximately a 50% cost savings for using fixed dosing as opposed to weight-based dosing.[4]

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TABLE 2. Definitions of Major Bleeding and Effective Hemostasis Used in Each Study

Source	Major Bleeding Definition	Hemostatic Efficacy Definition
Kim et al (2020)[4]	Moderate bleeding = possibly requiring blood transfusion but no hemodynamic compromise Major bleeding = intracranial hemorrhage or bleeding that causes hemodynamic compromise	Determined to be effective if: no further reports of significant bleeding in operative or procedural documentation, stabilization of bleeding noted on serial computed tomography scans, and no further significant drop in repeat hemoglobin measurements defined as a drop of > 2g/dL within 2-6 hours post PCC administration
Milioglou et al (2021)[5]	ISTH definition (17/33 studies), ANEXXA-4 trial8 criteria for hemostasis (5/33 studies),9 or each study's definition following center-specific or subjective information	
Schulman et al (2018)[6]	ISTH definition	Good = less than one hour to cessation of bleeding with no additional coagulation intervention required Moderate = one to four hours until cessation of bleeding, with no additional coagulation intervention required Poor/none = more than four hours until cessation of bleeding and/or additional coagulation required
Wilsey et al (2021)[3]	Life-threatening bleeding or potentially life-threatening requiring emergent surgery or invasive procedure or bleeding requiring a blood transfusion	Effective hemostasis reflects definitions used in ANNEXA-4 and were adapted from Shulman et al to include "moderate" and "good" ratings as hemostatic success
Majeed et al (2017)[7]	ISTH definition of major bleeding in non-surgical patients	Effective or ineffective based on criteria published by the Standardization Subcommittee on the Control of Anticoagulation of the ISTH

4F-PCC = 4-factor prothrombin complex concentrate
ISTH major bleeding in non-surgical patients is defined as having a symptomatic presentation and 1 of the following[9]:

- *Fatal bleeding, and/or*
- *Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or*
- *Bleeding causing a fall in hemoglobin level of 20 g L–1 (1.24 mmol L–1) or more or leading to transfusion of two or more units of whole blood or red cells*

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