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Fixed-Dose 4-Factor Prothrombin Complex Concentrate for Emergent Vitamin K Antagonist Reversal

Introduction

- Four factor prothrombin complex concentrate (4F-PCC) is FDA approved to reverse vitamin K antagonists (VKAs) such as warfarin in adult patients with acute major bleeding or a need for an urgent surgery/invasive procedure.
- 4F-PCC, also known as Kcentra®, contains factors II, VII, IX, and X, protein C and S, albumin, and small amounts of heparin.
- Fresh frozen plasma (FFP) is an alternative to Kcentra for the reversal of warfarin. **Compared to FFP, 4F-PCC:**
  - **Has a smaller volume, does not require thawing or ABO compatibility testing, has no risk of transfusion reactions**
  - **Is faster in reversing INR**
  - **Is more expensive (~$2,000-$8,000 per dose *vs* ~$50 per unit of FFP)**
- The package insert for Kcentra® indicates dosing is to be based on both INR and weight, resulting in possible confusion and delayed time to administration of Kcentra®.
- Multiple fixed-dose protocols have been proposed and analyzed including 500, 1000, 1500, or 2000 units.

KCentra® Pharmacology				
Properties	Contains factors II, XII, IX, and X as well as antithrombotic proteins C and S			
Dosing According to Package Insert	**Pre-treatment INR**	2 – 3.9	4 – 6	> 6
	Dose of Kcentra	25 units/kg	35 units/kg	50 units/kg
	Maximum dose	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000
Administration	Package insert recommends administering at a rate of ~3 units/kg/min (over about 5-10 minutes), though multiple sites report giving via IV push.			
PK/PD	INR is expected to decrease within 15-30 minutes, with effects lasting approximately 6-8 hours.			
Adverse Effects	Headache, nausea/vomiting, hypotension, stroke, pulmonary embolism, deep vein thrombosis			
Warnings	**Black box warning:** thromboembolic events (higher in patients with prior event); Kcentra® was not studied in patients with a thromboembolic event including myocardial infarction, cerebral vascular accident, unstable angina, etc in the prior 3 months **Serious adverse events:** stroke, pulmonary embolism, deep vein thrombosis			
	Hypersensitivity reactions, headache, nausea/vomiting, arthralgia, hypotension Kcentra® **contains heparin** and therefore is contraindicated in patients with known heparin induced thrombocytopenia (HIT)			
Compatibility	Administer in dedicated line – do not mix with other infusions			
Comments	Repeat INR 15-30 minutes after end of infusion. Vitamin K should be administered concomitantly to maintain prolonged INR reduction.			

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Overview of Evidence

Author, Year	Design (Sample Size)	Intervention & Comparison	Outcomes
Khorsand et al., 2012	Prospective observational (n=240)	Fixed dose 4F-PCC 1040 units vs variable-based dosing (median dose 1,560 units) **Excluded:** intracranial bleeding	• **No difference with fixed vs variable dosing in INR <2** measured 15 minutes after infusion: 91.7% *vs* 94.7% • Fixed dosing was non-inferior when looking at **clinical outcomes** (no visible bleeding, no further drop in Hgb, normalized blood pressure): 96% *vs* 88 • Time to dose: **130 *vs* 160 minutes** (*p*=0.015)
Klein et al, 2015	Retrospective review, (n=39)	Fixed dose 4F-PCC 1500 units vs variable-based dosing	• **INR ≤1.5: 71.8% with fixed dose** • **INR ≤2**: **92.3% with fixed dose** • $1,032 per patient was saved using fixed-dose
Abdoellakhan et al., 2016	Retrospective review, (n=53)	Fixed dose 4F-PCC 1000 units vs variable-based dosing (median dose 1750 units)	• **Fixed dose was more effective at obtaining INR ≤1.5:** 68% *vs* 96% (*p*=0.013) • No significant difference for patients presenting with an **INR ≤4** • **Additional dose given was more frequent with fixed dose regimen:** 32% *vs* 9% (*p*=0.043) • Time to dose: 60 *vs* 81 minutes (**p=0.773**)
Astrup et al., 2017	Retrospective review, (n=37)	Fixed dose 4F-PCC 1500 units vs variable-based dosing	• **INR ≤1.5** measured within 3 hours**: 74.3% with fixed dose** • **INR ≤2** measured within 3 hours: **100% with fixed dose** • Time to dose: 38 *vs* 51 minutes (**p=0.005**) • $982 per patient was saved using fixed-dose
Dietrich et al., 2020	Multi-center observational study (n=191)	Fixed dose 4F-PCC 1500 units (increase dto 2000 units if INR ≥7.5, TBW ≥100 kg or ICH) vs variable-based dosing	• **No difference in obtaining INR ≤1.4 (65 vs 57%, p=0.32)** • No difference in hospital length-of-stay, cost of therapy & thromboembolic complications
Stoecker et al., 2021	Prospective, open-label RCT, (n=113)	Fixed dose 4F-PCC 1500 units vs variable-based dosing	• **Reversal success to goal INR ≤1.5 was significantly lower with fixed dosing: 61.8 vs 89.2% (p=0.011)**
McMahon et al., 2021	Retrospective review, (n=54)	Fixed dose 4F-PFF 1000 units(non-CNS bleeds with INR ≤6) or 2000 units (CNS bleeds & non-CNS bleeds with INR ≥6.1) vs variable-based dosing	• No difference in target INR obtainment in CNS bleeds or non-CNS bleeds with INR ≥6.1 (p=0.52, p=0.21) • **Variable dosing was more effective in non-CNS patients with INR ≤6 (p=0.0002)**
Mohammadi et al., 2021	Systematic review & meta-analysis, (n=988)	10 studies included evaluating fixed vs variable-based dosing 4F-PCC dosing	• **Fixed dose was associated with lower rate of mortality (RR 0.65, 95% CI 0.47 -0.9, p=0.009)** • No difference in thromboembolic event rate (p=0.826) • **Fixed dose was less successful at obtaining lower INR goal (RR 0.87, 95% CI 0.78-0.96, p=0.007)**
Elsamadisi et al., 2021	Retrospective review, (n=44)	Fixed dose 4F-PCC 2000 units vs variable-based dosing	• **No significant difference in the primary outcome between both groups**
Dietrich et al., 2021	Retrospective, observational, multicenter study (n=90)	Fixed dose 4F-PCC 2000 units vs variable-based dosing (mediun dose 2000 units)	• **No difference in obtaining target INR ≤1.4 (82.6 vs 81.5%, p=0.14)** • Fixed-dose patients received higher doses than variable-based dosing (27 units/kg vs 24.5 units/kg)

Conclusions

- A fixed dose of 1000 to 2000 units of 4F-PCC appears to be effective in reversing warfarin-associated bleeds.
- Higher doses (1500-2000 units) may be needed for patients with ICH, higher INR, or higher body weight.
- **Benefits of fixed dose 4F-PCC include effective reversal at lower doses, shorter infusion times and cost savings.**

References

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