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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
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
Gilbert et al, 2019	Retrospective review, (n=60)	Fixed dose 4F-PCC 1500 units for ICH, 1500 units other bleed type vs variable-based dosing	**No differences in post-treatment INR** • **INR <1.6: 90% vs. 86.7% (p=0.68)** • **INR <1.4: 73.3% vs. 50% (p=0.06)** • **Median INR (IQR): 1.3 (1.1-19) vs. 1.35 (0.9-2.1) (p=0.16)**
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	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)**
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)
Abdoellakhan et al, 2022	RCT (n=199)	Fixed dose 4F-PCC 1000 units vs variable-based dosing	• **No difference in obtaining effective hemostasis, 87.3% vs 89.9%** • **Median door-to-needle times were faster in the fixed dosing group by 33 mins** • **No difference in obtaining INR <2 at 60 mins**

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

1. Kcentra (prothrombin complex concentrate [Human]) [package insert]. Kankakee, IL: CSL Behring LLC; 2013.
2. Tomaselli, Gordon F., et al. "2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways." Journal of the American College of Cardiology 70.24 (2017): 3042-3067.
3. Schwebach, Alyson A., Ryan A. Waybright, and Thomas J. Johnson. "A Review of Fixed-Dose Four-Factor Prothrombin Complex Concentrate for Vitamin K Antagonist Reversal: Does One Dose Fit All?." Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy (2019).
4. Khorsand, Nakisa, et al. "An observational, prospective, two-cohort comparison of a fixed versus variable dosing strategy of prothrombin complex concentrate to counteract vitamin K antagonists in 240 bleeding emergencies." haematologica 97.10 (2012): 1501-1506.
5. Abdoellakhan, Rahat Amadkhan, et al. "Fixed versus variable dosing of prothrombin complex concentrate in vitamin K antagonist-related intracranial hemorrhage: a retrospective analysis." Neurocritical care 26.1 (2017): 64-69.
6. Klein L, Peters J, Miner J, Gorlin J. Evaluation of fixed dose 4-factor prothrombin complex concentrate for emergent warfarin reversal. Am J Emerg Med. 2015;33(9):1213-1218.
7. Astrup G, Sarangarm P, Burnett A. Fixed dose 4-factor prothrombin complex concentrate for the emergent reversal of warfarin: a retrospective analysis. J Thromb Thrombolysis. 2018;45(2):300-305.
8. Dietrich, Mixon, Holowatyj et al. Multi-centered evaluation of a novel fixed-dose four-factor prothrombin complex concentrate protocol for warfarin reversal. Am J Emerg Med. 2020;38(10):2096-2100.
9. Stoecker, Van Amber, Woster et al. Evaluation of fixed versus variable dosing of 4-factor prothrombin complex concentrate for emergent warfarin reversal. Am J Emerg Med. 2021;48:282-287.
10. McMahon, Halfpap, Zhao et al. Evaluation of a fixed-dose regimen of 4-factor prothrombin complex concentrate for warfarin reversal. Ann Pharmacother. 2021. [Epub ahead of print]
11. Elsamadisi P, Cepeda MAG, Yankama T, Wong A, Tran Q, Eche IM. Weight-Based Dosing Versus a Fixed-Dose Regimen of 4-Factor Prothrombin Complex Concentrate in Obese Patients Requiring Vitamin K Antagonist Reversal. Am J Cardiovasc Drugs. 2021 May;21(3):355-361. doi: 10.1007/s40256-020-00442-w. Epub 2020 Nov 5. PMID: 33150496.
12. Mohammadi, Yaribash, Mohmood, Talasaz. Efficacy and safety of the fixed-dose versus variable-dose of 4-PCC for vitakmin K antagonist reversal: a comprehensive systematic review and meta-analysis. Cardiovasc Drug Ther. 2021. [Epub ahead of print]
13. Dietrich SK, Mixon MA, Rech MA. Fixed-dose prothrombin complex concentrate for emergent warfarin reversal among patients with intracranial hemorrhage. Am J Emerg Med. 2021 Jun 26;49:326-330. doi: 10.1016/j.ajem.2021.06.032. Epub ahead of print. PMID: 34224954.
14. Gilbert BW et al. Modified Version of the American College of Cardiology's Recommendation for Low-Dose Prothrombin Complex Concentrate is Effective for Warfarin Reversal. Am J Emerg Med 2019;X(XX):1-4.
15. Abdoellakhan RA, Khorsand N, Ter Avest E, Lameijer H, Faber LM, Ypma PF, Nieuwenhuizen L, Veeger NJGM, Meijer K. Fixed Versus Variable Dosing of Prothrombin Complex Concentrate for Bleeding Complications of Vitamin K Antagonists-The PROPER3 Randomized Clinical Trial. Ann Emerg Med. 2022 Jan;79(1):20-30.