Kcentra® (Prothrombin Complex Concentrate [Human]): Its indications, side effects, and contraindications

Amr Ismail MD

ABSTRACT

Patients with a high risk for thromboembolic events can be on long-term warfarin. These patients need close monitoring of their INR and for signs of bleeding. Conventionally, fresh frozen plasma (FFP) is used for reversal of INR in patients with major bleeding or who need urgent surgery or invasive procedures. Kcentra is now available as an alternative to FFP for rapid reversal of INR and urgent hemostasis.

Keywords: Kcentra, four factor prothrombin complex concentrate, acute major bleeding, urgent hemostasis, INR reversal, warfarin

INTRODUCTION

Kcentra is a purified, heat-treated, nanofiltered, and lyophilized non-activated four-factor Prothrombin Complex Concentrate (Human) prepared from human U.S. Source Plasma (CSL Behring, King of Prussia, PA). It contains the Vitamin K dependent coagulation factors II, VII, IX, and X and antithrombotic Proteins C and S. Factor IX is the key factor for its potency. Its constituents include human antithrombin III, heparin, human albumin, sodium chloride, and sodium citrate. Kcentra is sterile, pyrogen-free, and does not contain preservatives. It is used for urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonists (warfarin) in adults with acute major bleeding or a need for urgent surgery or invasive procedures.[1]

Corresponding author: **Amr Ismail**
Contact Information: Amr.ismail@ttuhsc.edu
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PHARMACOLOGY

Patients at high risk for thromboembolic events are often started on warfarin to decrease vitamin K dependent activation of clotting factors in the liver, including II, VII, IX, X, and the antithrombotic Proteins C and S. Warfarin has a narrow therapeutic window, and multiple interactions affect its activity.[2] Conventionally, fresh frozen plasma (FFP) is used for warfarin induced coagulation factor deficiency. Fresh frozen plasma has a very high volume, potentially causing volume overload, requires long infusion times, increases the risk of allergic or anaphylactic reaction, and carries a risk for transfusion related acute lung injury (TRALI).[3,4] Kcentra is 25 times more concentrated than FFP.[5] It has 85% less volume and is transfused seven times faster than FFP. Kcentra contains non-activated clotting factors, allowing the body to activate only what is needed (1).

Monitoring of Kcentra: Monitor patients receiving Kcentra for signs and symptoms of thromboembolic events. Resumption of anticoagulation should be carefully considered as soon as the risk of thromboembolic events outweighs the risk of acute bleeding.[1]

Advantages: No need for cross matching; 36-month room temperature storage; rapid administration with low volume of infusion (85% less volume than FFP); sustained INR reductions for up to 24 hours; and individualized Kcentra dosing depending on body weight and pre-dose INR can be done.[1]

Contraindications: Anaphylactic or severe systemic reaction to Kcentra or any of its constituents; DIC; known HIT.[1]

Adverse reactions: Adverse reactions were defined as those occurring within 72 hours of infusion plus events considered probably/possibly related or related to the treatment.[1] These included fatal and non-fatal arterial and venous thromboembolic complications, stroke, PE, and DVT. The most frequent adverse reactions were headache, nausea/vomiting, hypotension, and anemia (≥2.8%). The most serious adverse events were thromboembolic events, including stroke, pulmonary embolism, and DVT.

It has not been studied in patients who had a thromboembolic event, myocardial infarction, DIC, CVA, TIA, unstable angina pectoris, or severe peripheral vascular disease within 3 months. The safety of

Table 1. Adverse reactions reported in more than 5 subjects (≥2.8%) following Kcentra or FFP administration in acute major bleeding RCT[6]

Adverse reactions	No. (%) of subjects	
	Kcentra (N = 191)	Plasma (N = 197)
Nervous system disorders		
Headache	14 (7.3%)	7 (3.6%)
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	8 (4.2%)	3 (1.5%)
Respiratory distress/dyspnea/hypoxia	7 (3.7%)	10 (5.1%)
Pulmonary edema	3 (1.6%)	10 (5.1%)
Gastrointestinal disorders		
Nausea/vomiting	12 (6.3%)	8 (4.1%)
Diarrhea	4 (2.1%)	7 (3.6%)
Cardiac disorders		
Tachycardia	9 (4.7%)	2 (1.0%)
Atrial fibrillation	8 (4.2%)	6 (3.0%)
Metabolism and nutrition disorders		
Fluid overload*	5 (2.6%)	16 (8.1%)
Hypokalemia	9 (4.7%)	14 (7.1%)
Psychiatric disorders		
Insomnia	9 (4.7%)	6 (3.0%)
Vascular disorders		
Hypotension**	14 (7.3%)	10 (5.1%)
Injury, poisoning, and procedural complications		
Skin laceration/contusion/subcutaneous hematoma	8 (4.2%)	5 (2.5%)
Blood and lymphatic disorders		
Anemia ||	11 (5.8%)	16 (8.1%)

*Includes fluid overload and cardiac failure congestive; **Includes orthostatic hypotension, hypotension, and hemorrhagic shock
|| Includes anemia, hemoglobin decreased, and hematocrit decreased; Accessed from package insert with written permission from CSL Behring.

Kcentra has not been studied in children or pregnant women. Repeat dosing with Kcentra is not supported by clinical data and is not recommended. Finally, there is a theoretical risk of transmitting infectious agents despite two dedicated virus reduction steps.

Thromboembolic events occurred more frequently following Kcentra compared to FFP in a randomized, plasma controlled trial in subjects requiring urgent reversal of VKA anticoagulation due to acute major bleeding. The excess in thromboembolic events was more pronounced among subjects who had a history of prior thromboembolic events, although these differences were not statistically significant. Potential benefits of treatment with Kcentra should be weighed against the potential risks of thromboembolic events.[1]

Clinical trials

Two major studies were cited by the FDA for approval of this product.

Randomized, plasma-controlled trial in acute major bleeding: This prospective randomized control, multicenter trial enrolled 212 subjects who required urgent reversal of VKA therapy due to acute major bleeding; 103 were treated with Kcentra and 109 with FFP. The ages ranged from 26-96 years.[6]

In this trial, Kcentra was as effective as plasma in achieving effective hemostasis. It included patients on warfarin with INR ≥2 and major bleeding. Subjects with a history of a thrombotic event, myocardial infarction, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, severe peripheral vascular disease, or disseminated intravascular coagulation within the previous 3 months were excluded from the study.[6]

The efficacy endpoint was hemostatic efficacy for the time period from the start of infusion of Kcentra or FFP until 24 hours. Efficacy was adjudicated as "effective" or "not effective." Criteria for effective hemostasis were based upon standard clinical assessments, including vital signs, hemoglobin measurements, and CT assessments at pre-defined time points, relevant to the type of bleeding (i.e., gastrointestinal, intracranial hemorrhage, visible, musculoskeletal, etc.). An additional endpoint was the reduction of INR to ≤1.3 at 30 minutes after the end of infusion of Kcentra or FFP for all subjects who received study product (see Table 2 below).[6]

Randomized, Plasma-Controlled Trial in Urgent Surgery/Invasive Procedures: This prospective randomized control trial, multicenter enrolled 176 subjects who required urgent reversal of VKA therapy due to the need for an urgent surgical or urgent invasive procedure. Eighty-eight were treated with Kcentra and 88 with FFP. The ages ranged from 27-94 years. The same exclusion criteria were used as the acute bleeding study.[7]

The primary endpoint was effective hemostasis, and the co-primary endpoint was rapid INR reduction (≤1.3 at 0.5 h after infusion end). Adverse events and serious adverse events were reported to days 10 and 45, respectively.[7]

This study showed that Kcentra is non-inferior and is superior to FFP for rapid INR reversal and effective hemostasis in patients needing VKA reversal for urgent surgical or invasive procedures. The safety profile of Kcentra was generally similar to that of FFP.[7]

Table 2. Median INR after start of infusion in acute major bleeding study[6]

Treatment	Baseline	30 min	1 hr	2-3 hr	6-8 hr	12 hr	24 hr
Kcentra (N = 98)	3.90 (1.8-20.0)	1.20* (0.9-6.7)	1.30* (0.9-5.4)	1.30* (0.9-2.5)	1.30* (0.9-2.1)	1.20* (0.9-2.2)	1.20 (0.9-3.8)
Plasma (N =104)	3.60 (1.9-38.9)	2.4 (1.4-11.4)	2.1 (1.0-11.4)	1.7 (1.1-4.1)	1.5 (1.0-3.0)	1.4 (1.0-3.0)	1.3 (1.0-2.9)

*Statistically significant difference compared to plasma by 2-sided Wilcoxon test in Study 3002 INR = international normalized ratio. Accessed from package insert with written permission from CSL Behring.

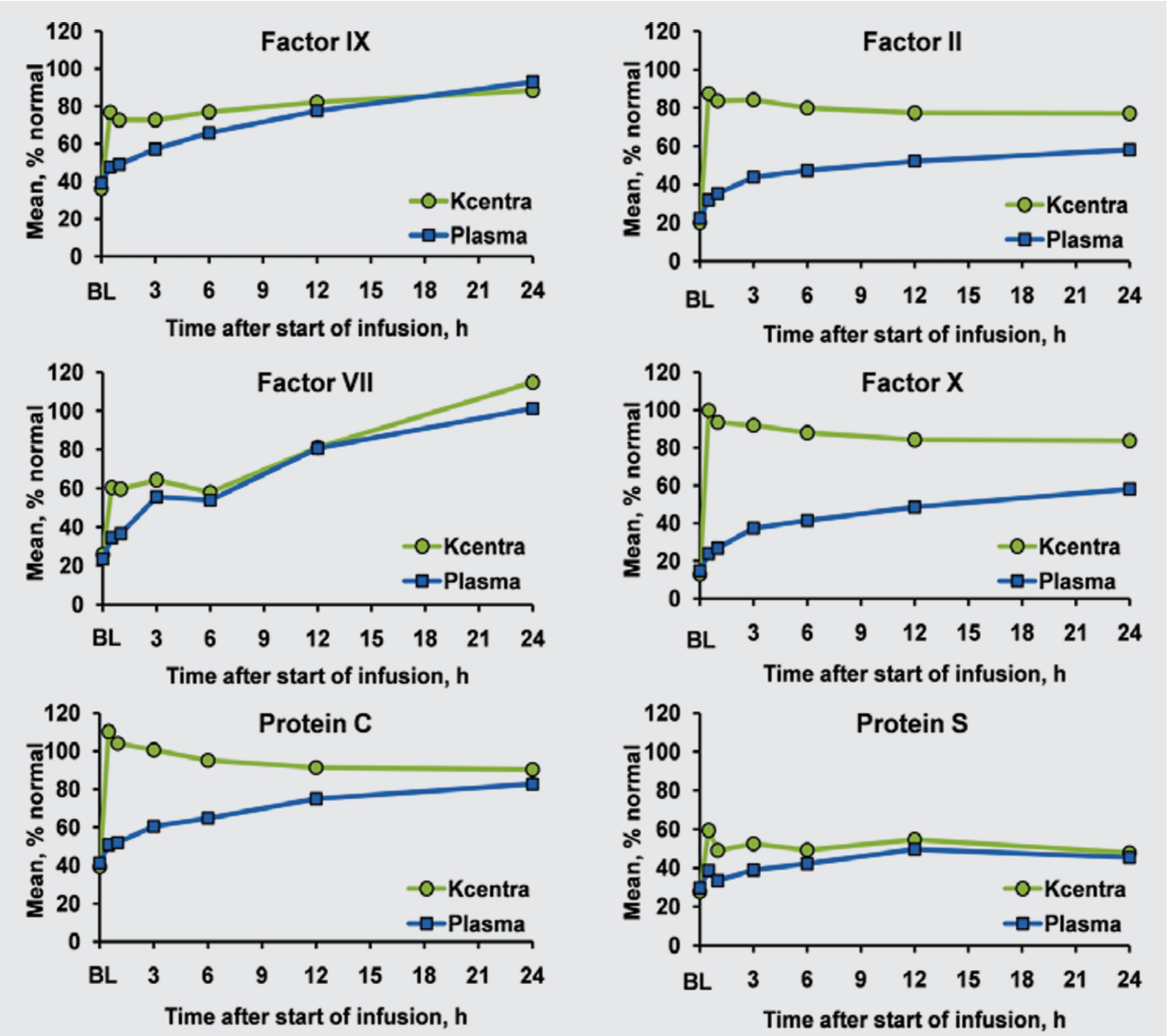

Figure 1. The increase in mean factor levels over time following Kcentra and plasma administration in the plasma-controlled RCT in acute major bleeding is shown in the above figure.[6] Accessed on 6-10-2017 from package insert with written permission from CSL Behring.

The relationship between INR values and clinical hemostasis in patients has not been established.

Key points

1. Kcentra is used for urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonists.
2. It is FDA approved for use in patients with acute major bleeding or who need urgent surgery or invasive procedures.
3. It achieves earlier hemostasis using INR reduction and clinical hemostasis as end-points than FFP. The relationship between INR values and clinical hemostasis has not been established.

4. Most common adverse effects noted are headache, nausea/vomiting, hypotension, and anemia.
5. The most serious adverse events are thromboembolic events, including stroke, pulmonary embolism, and DVT. Patients with thromboembolic events within three months were excluded from the studies used for product approval. Its safety profile among this patient population is not well studied, and it is generally avoided.
6. Kcentra offers a low volume, fast method for rapid INR reversal and clinical hemostasis. Its increased use will further define its safety profile and possibly identify other indications.

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References

1. KCENTRA (package insert). Kankakee, IL: CSL Behring; 2017.
2. Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012 Feb;141(2 Suppl):e44S–e88S.
3. Pandey S, Vyas GN. Adverse effects of plasma transfusion. Transfusion 2012 May; 52 Suppl 1:65S–79S.
4. Theusinger OM et al. Point of Care and Factor Concentrate-Based Coagulation Algorithms. Transfus Med Hemother 2015 Mar;42(2):115–121.
5. Schulman S, Bijsterveld NR. Anticoagulants and their reversal. Transfus Med Rev 2007;21(1):37–48.
6. Sarode R, Milling TJ, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013;128:1234–43.
7. Goldstein JN, Refaai MA, Milling TJ Hr, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomized control study. Lancet 2015 May 23;385(9982):2077–87.