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, randomised trial

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Summary

Background Rapid reversal of vitamin K antagonist (VKA)-induced anticoagulation is often necessary for patients needing urgent surgical or invasive procedures. The optimum means of VKA reversal has not been established in comparative clinical trials. We compared the efficacy and safety of four-factor prothrombin complex concentrate (4F-PCC) with that of plasma in VKA-treated patients needing urgent surgical or invasive procedures.

Methods In a multicentre, open-label, phase 3b randomised trial we enrolled patients aged 18 years or older needing rapid VKA reversal before an urgent surgical or invasive procedure. We randomly assigned patients in a 1:1 ratio to receive vitamin K concomitant with a single dose of either 4F-PCC (Beriplex/Kcentra/Confidex; CSL Behring, Marburg, Germany) or plasma, with dosing based on international normalised ratio (INR) and weight. The primary endpoint was effective haemostasis, and the co-primary endpoint was rapid INR reduction (≤1·3 at 0·5 h after infusion end). The analyses were intended to evaluate, in a hierarchical fashion, first non-inferiority (lower limit 95% CI greater than –10% for group difference) for both endpoints, then superiority (lower limit 95% CI >0%) if non-inferiority was achieved. Adverse events and serious adverse events were reported to days 10 and 45, respectively. This trial is registered at ClinicalTrials.gov, number NCT00803101.

Findings 181 patients were randomised (4F-PCC n=90; plasma n=91). The intention-to-treat efficacy population comprised 168 patients (4F-PCC, n=87; plasma, n=81). Effective haemostasis was achieved in 78 (90%) patients in the 4F-PCC group compared with 61 (75%) patients in the plasma group, demonstrating both non-inferiority and superiority of 4F-PCC over plasma (difference 14·3%, 95% CI 2·8–25·8). Rapid INR reduction was achieved in 48 (55%) patients in the 4F-PCC group compared with eight (10%) patients in the plasma group, demonstrating both non-inferiority and superiority of 4F-PCC over plasma (difference 45·3%, 95% CI 31·9–56·4). The safety profile of 4F-PCC was generally similar to that of plasma; 49 (56%) patients receiving 4F-PCC had adverse events compared with 53 (60%) patients receiving plasma. Adverse events of interest were thromboembolic adverse events (six [7%] patients receiving 4F-PCC *vs* seven [8%] patients receiving plasma), fluid overload or similar cardiac events (three [3%] patients *vs* 11 [13%] patients), and late bleeding events (three [3%] patients *vs* four [5%] patients).

Interpretation 4F-PCC is non-inferior and superior to plasma for rapid INR reversal and effective haemostasis in patients needing VKA reversal for urgent surgical or invasive procedures.

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Introduction

Patients receiving therapy with a vitamin K antagonist (VKA) have an increased risk of bleeding during surgical and procedural interventions.[1] Therefore, guidelines recommend temporary interruption of VKA therapy 5 days before elective surgery to minimise perioperative bleeding.[1] However, when patients need an urgent procedure, VKA reversal is often performed in the acute setting. Findings from a 2012 clinical trial underlined the risks involved, showing that the frequency of periprocedural bleeding in patients receiving VKA therapy was 3·3% for elective procedures, but 21·6% for emergency procedures.[2] Although vitamin K alone can be effective, reversal can take several hours.[3] Therefore, emergency reversal additionally necessitates the rapid replacement of vitamin K-dependent coagulation factors (ie, factors II, VII, IX, and X).

In some countries, including the USA, plasma is the most commonly used agent for rapid VKA reversal. Although plasma contains the vitamin K-dependent coagulation factors, it needs ABO typing and thawing before use, and is associated with long infusion times.[4–6] More importantly, it can be associated with severe adverse outcomes including transfusion-related acute lung injury and transfusion-associated circulatory overload.[7] Non-activated prothrombin complex concentrates contain vitamin K-dependent coagulation factors and are categorised as three-factor (3F-PCC) or four-factor (4F-PCC) prothrombin complex concentrates (depending

on whether they contain clinically relevant amounts of factor VII).[8] Prothrombin complex concentrates are stored at room temperature as a lyophilised powder, do not need ABO typing, can be prepared within minutes, and can be delivered in smaller volumes with shorter infusion times than can plasma.[4]

Adequately powered comparative trials investigating the optimum means of VKA reversal have not been done in patients needing urgent interventions, and the best method to promptly reverse VKAs remains unclear. The only plasma-controlled randomised clinical trial was a single-centre study of 40 patients (20 per group) undergoing semiurgent cardiac surgery, which was underpowered to detect significant differences in haemostatic efficacy.[9] We therefore did a randomised clinical trial to compare 4F-PCC with plasma for urgent VKA reversal in patients needing urgent surgical or invasive procedures.

Methods

Study design and participants

In a randomised, open-label, active-controlled, non-inferiority, multicentre, phase 3b clinical trial, we enrolled patients in 33 hospitals (18 in the USA, two in Belarus, four in Bulgaria, two in Lebanon, one in Romania, and six in Russia).

Patients with an international normalised ratio (INR) of 2·0 or higher receiving VKA therapy and needing an urgent surgical or invasive procedure within 24 h were eligible for the study. The decision about the need for surgical treatment and rapid VKA reversal was made by the clinical care teams. Exclusion criteria included requirement for a procedure for which an accurate estimate of blood loss was not possible (eg, ruptured aneurysm or trauma) or coagulopathy that could be corrected solely through administration of vitamin K and withdrawal of VKA therapy. Full inclusion and exclusion criteria are provided in the appendix.

See Online for appendix

As part of ongoing review of the investigational new drug application, the United States Food and Drug Administration (FDA) reviewed the study protocol after the trial had been initiated. On July 20, 2011, after 157 patients had been enrolled, the FDA requested that enrolment of patients needing non-surgical invasive procedures be halted because of concern that no differences in haemostatic efficacy would be detected. No interim safety or efficacy analysis was done at this time. Sites were notified via letter on July 26, 2011, to immediately cease enrolment of this population, and a final protocol amendment was made on Sept 7, 2011. Patients needing urgent surgical procedures continued to be enrolled as planned.

The study was approved by the independent ethics committees and institutional review boards of the participating centres, in accordance with local legal requirements; written informed consent was obtained from all patients.

Randomisation and masking

Investigators called a 24 h randomisation centre and transmitted deidentified data for the randomisation procedure. We randomly assigned patients in a 1:1 ratio using a computerised system to receive either 4F-PCC (Beriplex/Kcentra/Confidex; CSL Behring, Marburg, Germany) or plasma. Treatment assignment was done by a centrally managed, biased-coin minimisation method,[10] which is an adaptive randomisation scheme (appendix). This method also controlled for balance, both overall and within centres, between treatment groups within urgent surgical or invasive procedures with use of two levels of stratification: one based on the type of procedure, and one on the vitamin K dose given.

The first level of strata was: all cranial neurosurgical procedures; all cardiothoracic surgical procedures; all major orthopaedic surgical procedures (eg, open reduction internal fixation of hip); all other surgical procedures (such as general surgery, ear-nose-throat, noncranial neurological [eg, spine procedures], urological, gynaecological, cardiovascular [eg, femoropopliteal bypass procedures], and minor orthopaedic interventions [eg, open reduction of ulna fracture]); and all invasive procedures (recruitment to this category was halted after protocol amendment). The second level of strata was oral vitamin K dose less than or equal to 2 mg; oral vitamin K dose more than 2 mg; and any intravenous vitamin K dose.

Surgery type was classified by the treating physician according to the first level of strata. The trial was open label; clinicians, study staff, and trial participants could not be blinded to treatment allocation because of the inherent characteristics of the study agents. The safety adjudication board (described below) was masked to treatment allocation.

Procedures

On day 1, patients received an intravenous infusion of study treatment based on baseline INR (assessed ≤3 h before start of infusion) and bodyweight, as described by Sarode and colleagues.[11] Patients with baseline INR of 2 or higher but lower than 4 were given 4F-PCC at a dose of 25 IU factor IX per kg bodyweight or plasma 10 mL/kg bodyweight; those with baseline INR of 4 to 6 (inclusive) were given 4F-PCC at a dose of 35 IU factor IX per kg or plasma 12 mL/kg; and those with baseline INR higher than 6 were given 4F-PCC at a dose of 50 IU factor IX per kg or plasma 15 mL/kg. Patients weighing more than 100 kg were given doses based on a bodyweight of 100 kg.

4F-PCC was given at an infusion rate of 3 IU/kg per min or less; plasma was infused as rapidly as possible and at the discretion of the treating clinical team. Thus, the plasma infusion rate represented standard care and maximised patient safety (because of concern that some patients might not be able to tolerate rapid volume load). Additionally, vitamin K was to be given to all patients according to American College of Chest Physicians[12] guidelines (≤5 mg orally, followed by 1–2 mg orally if