



Review Article

Systematic review: 3-factor versus 4-factor prothrombin complex concentrate for warfarin reversal: Does it matter?

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ABSTRACT

Introduction: Prothrombin complex concentrates are used for rapid reversal of vitamin K antagonists in patients with bleeding or those requiring surgery or invasive procedures. Current guidelines suggest 4-factor products are preferred over 3-factor prothrombin complex concentrates.

Materials and Methods: We performed a systematic review comparing the effectiveness of 3-factor to 4-factor prothrombin complex concentrates in normalizing the international normalized ratio to ≤ 1.5 in patients with acquired coagulopathy due to vitamin K antagonist use. Studies reporting administration of prothrombin complex concentrates for emergent reversal of vitamin K antagonists that included results of baseline prothrombin time/international normalized ratio and follow-up testing within 60 minutes of prothrombin complex concentrates administration were included.

Results: A total of 18 studies were included representing 654 patients. The most common indications for prothrombin complex concentrate were intracerebral hemorrhage, urgent surgery or invasive procedure, and gastrointestinal bleeding. Baseline international normalized ratio values ranged from 3.3–5.1 in the 3-factor group and from 2.3 to greater than 20 in the 4-factor group. The international normalized ratio repeated within one hour of prothrombin complex concentrates administration ranged from 1.2–1.9 in the 3-factor group and 1.0–1.9 in the 4-factor group. International normalized ratio decreased to ≤ 1.5 within one hour after prothrombin complex concentrates administration in 6 of 9 studies in the 3-factor group, and 12 of 13 studies in the 4-factor group.

Conclusion: More reliable correction of the international normalized ratio was seen with 4-factor compared to 3-factor prothrombin complex concentrates which may have clinical implications since 4-factor products are unavailable in some countries.

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Abbreviations: INR, international normalized ratio; PCC, prothrombin complex concentrate; PT, prothrombin time; VKA, vitamin K antagonist.

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Introduction

Prothrombin complex concentrates (PCC), also known as factor IX complex concentrates, are commonly used to reverse the effects of vitamin-K antagonists (VKA) in patients with bleeding and those requiring invasive procedures or surgery. All PCCs contain the vitamin K-dependent coagulation factors II, IX and X, with variable amounts of factor VII. Products are categorized as either 3-factor or 4-factor PCCs based on the relative factor VII content. Some formulations also contain protein C, protein S, protein Z, antithrombin III, and/or heparin. PCCs offer several advantages over fresh frozen plasma (FFP) including faster normalization of the international normalized ratio (INR), smaller infusion volume, rapid administration, and no requirement for ABO blood-type matching. All PCC products are derived from pooled plasma and carry the possible risk of virus transmission, although the risk is considered very low due to improved methods of virus inactivation.

International guideline statements recommend the use of PCCs when rapid reversal of anticoagulation is indicated in patients with major bleeding due to VKA use [1–5]. Numerous studies have found that PCCs rapidly normalize the INR to a value of less than 1.5, typically within 10–30 minutes [6]. However, many of these studies utilized 4-factor PCC formulations that are not available in many countries and some experts specifically recommend 4-factor PCCs for VKA-associated major bleeding, although this recommendation is based mostly on observational data [5].

Recently the effectiveness of 3-factor PCCs have been questioned due to subtherapeutic (or no) factor VII, which may affect the ability to reverse the INR [7]. A study by Holland et al. reported the use of 25 (low dose) or 50 (high dose) IU/kg of a 3-factor PCC (Profilnine-SD) in

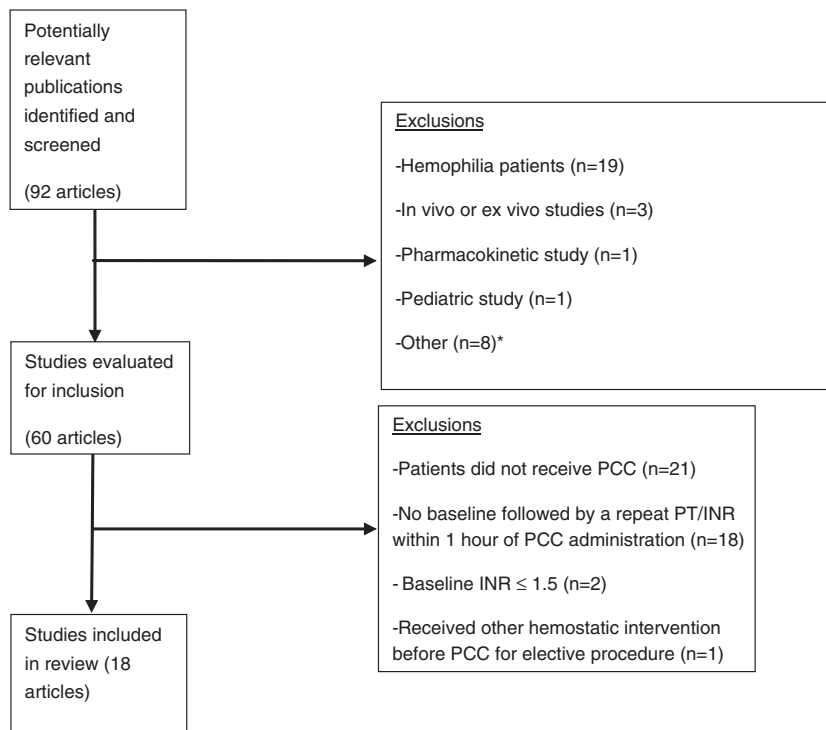
40 patients with baseline INR >5.0 and either bleeding or high-risk of bleeding [8]. Patients with intracerebral hemorrhage (ICH) were excluded and the most common site of bleeding was gastrointestinal. The primary endpoint was INR less than 3.0 within 24 hours of PCC administration. Only 55% and 43% of patients in the low dose and high dose groups achieved the primary endpoint. Limitations of this study include the retrospective design and very low use of intravenous vitamin K, which may have impacted INR correction since the effect of PCC may be transient while vitamin K invokes a sustained rise in clotting factor concentrations. To our knowledge, there are no published studies comparing the effectiveness of 3-factor and 4-factor PCCs for reversal of anticoagulation. The purpose of this systematic review is to compare the effectiveness of 3-factor to 4-factor PCCs in normalizing the INR to ≤ 1.5 in patients with an acquired coagulopathy due to VKA use.

Materials and methods

The systematic review was performed utilizing the methodology from the PRISMA Statement and no specific protocol or registry was used [9].

Search strategy

We searched the MEDLINE database from 1966 to November 2011 using the following strategy: ("prothrombin complex concentrates" [Supplementary Concept] OR "Factor IX"[Mesh]) AND "Anticoagulants" [Pharmacological Action]). This search revealed 813 potentially relevant articles. The search was then limited by adding the terms ("Clinical Trial"[Publication Type] OR "Case-control Studies"[Mesh]) OR "Cohort Studies"[Mesh]) which resulted in 85 potentially relevant articles. We



*Most common: case report or duplicate study.

Fig. 1. Study flow diagram. *Most common: case report or duplicate study.

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