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CAT Block 2

Reference: Milling, Truman et al. "Safety of a Four-factor Prothrombin Complex Concentrate Versus Plasma for Vitamin K Antagonist Reversal: An Integrated Analysis of Two Phase IIIb Clinical Trials." *Academic Emergency Medicine*: Volume 23, Issue 4, Pages 466–475, 2016.

Question: Is the safety profile of plasma vs four-factor prothrombin complex concentrate the same in treatment of patients requiring vitamin K antagonists reversal for acute major bleeding or prior to urgent surgical/invasive procedure?

Introduction: Many patients in the US are currently treated with vitamin K antagonists and present to the ED with bleeding/urgent surgery and need for reversal. There are 3.4 million patients each year prescribed to patients for treatment and prophylaxis of prothrombotic conditions. Warfarin is associated with multiple adverse events requiring emergency treatment in patients over 65 years old. Most often it is due to bleeding and can result in over 33,000 hospitalizations per year. Currently plasma is the most commonly used agent for reversal in many countries. Prothrombin complex concentrates are not licensed for use in all countries. There is not much known about the safety profile of plasma (FFP) and four-factor prothrombin complex concentrate (4F-PCC). An integrated analysis of safety data from two clinical trials was done to compare the two treatments for vitamin K antagonist reversal.

Methods: The analysis comprised adverse event data from two phase IIIb, randomized, controlled trials. Studies were performed across 36 and 33 sites, in 9 countries, with analysis comprising of 388 patients. Patients were randomized in 1:1 fashion. For 4F-PCC, the n was 191, 197 for FFP. The patients had to be 18 years or older and had to require vitamin K antagonist reversal due to major bleeding or prior to urgent surgical/invasive procedures with an INR ≥ 2 during 3 hours prior to start of treatment. Patients received either 4F-PCC or FFP, dosed according to INR and body weight. 4F-PCC contained the non-activated factors II, VII, IX, and X, protein C and S. Patients also received vitamin K. Adverse events and serious adverse events were assessed at days 10 and 45. The endpoint of both studies was effective hemostasis with an INR reduction to ≤ 1.3 at 0.5 hours after end of infusion of medication.

Results: The proportion of patients with adverse events and serious adverse events were similar between groups. For 4F-PCC there were 115/191 (60.2%) adverse events and for plasma 124/197 (62.9%) adverse events. The most common adverse events include constipation, headache, peripheral edema, and hypotension for 4F-PCC, and hypokalemia, peripheral edema, anemia, and constipation for FFP. Serious adverse events included stroke, DVT, thrombosis, venous insufficiency, MI, fluid overload, pulmonary edema, and respiratory failure. Serious adverse events of 4F-PCC was 54/191 (28.3%), and 49/197 (24.9%) for FFP. Proportion of patients with thromboembolic events similar between groups, 4F-PCC was 14/191 (7.3%) and for FFP, 14/197 (7.1%). This is a difference of 0.2% (95% CI= -5.5 to 6). There were 13 deaths (6.8%) in 4F-PCC group and 13 (6.6%) in the FFP group. The difference in deaths between groups was 0.2% with a 95% CI of -5.3 to 5.8. Fluid overload occurred in more patients in the FFP group than 4F-PCC group, 25 (12.7%) and 9 (4.7%) respectively. The difference between groups is -8% with a 95% CI of -14.1 to -2.0. The median volume of 4F-PCC was 90 mL vs 800 mL in FFP group.

Conclusions: The safety profile of 4F-PCC compared to that of FFP for reversal of vitamin K antagonists was similar when comparing adverse events, serious adverse events, thromboembolic events, and death. It was, however, associated with fewer fluid overload events. This goes back to the fact that the patients receiving 4F-PCC received less fluid compared to the FFP group. Most patients receiving warfarin have other comorbidities that can make it unclear as to if the adverse events and death were due to the treatment or underlying issues and age.

Limitations: The two trials were not powered to support a comparison of safety between treatment groups in terms of significant differences. All comparison was done through differences in ranges and confidence intervals. Also, the clinicians and study investigators could not be blinded to treatment due to the difference in administration of FFP vs 4F-PCC.
