Effect of 4-prothrombin complex concentrate on mortality in patients presenting to the emergency department with warfarin-induced bleeding

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Abstract

Aim: Today, it has been observed that the increase in the use of vitamin K antagonists (VKA) causes various complications, from acute bleeding to death. Fresh frozen plasma and 4-prothrombin complex concentrate (4-PCC) are still used in the treatment of these patients. In our study, we aimed to investigate the effect of 4-PCC use on early mortality in patients presenting with bleeding due to VKA.

Material and Methods: Our study was conducted in a district state hospital with a retrospective and single-center design. It enrolled a total of 89 patients with a history of vitamin K antagonist drug use; patients with a history of trauma-induced hemorrhage or hematological disease were excluded.

Results: Out of 89 patients with a mean age of 71.00±10.79 years, 51.7% were male and 51.7% had a major hemorrhage and 48.3% had minor hemorrhage. Twenty-seven percent of the patients died despite treatment. The mean post-admission INR level was 9.48±5.8. Post-treatment and 24-hour INR levels were significantly lower in both patient groups treated with 4-PCC and FFP. It was determined that the administration of vitamin K did not lead to any significant difference in both patient groups treated with FFP and 4-PCC. Additionally, the treatment lasted 4 times longer, and the mortality rate was 4 times higher among patients treated with FFP than those treated with 4-PCC.

Discussion: We detected that the use of 4-PCC to reverse the anticoagulant effect will provide more rapid treatment, less volume loading, and lower mortality among patients using VKAs.

Keywords
Hemorrhage; Vitamin K Antagonist; Prothrombin Complex Concentrate

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Introduction
Vitamin K antagonists (VKAs) are currently among widely prescribed medications. Many studies in the literature have reported that these agents effectively treat and prevent many thromboembolic events [1]. However, these agents have a narrow therapeutic range, which may cause complications [2,3]. These complications include major hemorrhages such as intracranial hemorrhage and gastrointestinal hemorrhage and minor hemorrhages such as epistaxis, gingival bleeding, and hematuria [4,5]. The risk of hemorrhage particularly increases when the international normalized ratio (INR) level rises above 5.0 [5]. Therefore, patients using these agents frequently present to the emergency department with hemorrhage [6]. There are times when rapid intervention is required in patients who present to the emergency department with VKA-induced hemorrhage. In some of these conditions, such as intracranial bleeding requiring surgery or massive gastrointestinal bleeding requiring interventional procedures, it may be necessary to reverse the effect of CVA [7]. Although vitamin K administration is part of the routine procedure in such patients, it may take up to 4 hours in intravenous administration and 24 hours in oral administration for INR starting to fall [8-10].

Currently, fresh frozen plasma (FFP) is widely used to reverse the effects of VKAs. However, FFP has some disadvantages such as long preparation time, risk of transfusion reactions, and volume loading [11,12]. Four-prothrombin complex concentrate (4-PCC) contains factor 7 in addition to vitamin K-dependent coagulation factors 2, 9, and 10 [11,13]. Whereas normalizing INR with FFP is often difficult and takes a long time, 4-PCC fulfills this task quickly and effectively [11,14]. 4-PCC has been used to reverse the effect of VKAs for a long time now. International guidelines also recommended the use of 4-PCC for an urgent reversal of INR in VKA-induced hemorrhage [15].

In this study, we aimed to investigate the effect of the use of 4-PCC on early mortality among patients presenting with VKA-induced hemorrhage.

Material and Methods
Study Design
Our study retrospectively recorded the medical data of successive patients older than 18 years of age who presented to the emergency department with VKA-induced hemorrhage. The study participants were those who were known to be previously administered VKA agents against thromboembolic events. Early in-hospital mortality was recorded from patient records during the hospital stay.

Study Settings and Population
This study was designed to be conducted between January 1, 2018, and January 1, 2020, in the emergency department of a district state hospital with a capacity of approximately 500 emergencies per day and 150 beds. The study population was composed of patients older than 18 years with complete medical records, who presented to the emergency with VKA-induced hemorrhage. A hemorrhage was detected by an emergency medicine specialist.

Our study design excluded patients with traumatic hemorrhage, a history of the hematological disease, and an unclear history of VKA use. Patient records were obtained from the hospital automation system and medical records archive. In-hospital mortality was defined as death occurring within 7 days after hospital admission.

Study Protocol
Before the collection of the patients’ data, an ethics committee approval was obtained (ethics committee no. E-37201737-806.02.02). Patients using VKA who presented to the emergency department with acute hemorrhage were retrospectively identified with the help of the hospital data management system. Their age, sex, indications for VKA use, and outcomes were recorded from the hospital data management system. The same system was also used to record the treatments administered to the patients (vitamin K, fresh frozen plasma (10mL/kg), and 4-PCC (50 IU/kg)) and their duration of administration, patient outcomes (admission to a regular ward, admission to intensive care unit, or discharge), and mortality data. All data were recorded on previously prepared study forms.

Statistical Analysis
SPSS (Statistical Package for Social Sciences) for Windows 20.0 software was used for the statistical analysis of all the data obtained. All data were summarized in tables during evaluation. The Mann-Whitney U test was used to compare the mean values of the data obtained, and the Pearson Chi-Square (and the Fisher’s exact test when required) was used to compare non-parametric data. The results were considered significant at p<0.05, with a 95% confidence interval.

Results
Our study included 89 patients, of whom 43 (48.3%) were female and 46 (51.7%) were male. The mean age of the study population was 71.00±10.79 years. The indications for VKA use was a history of atrial fibrillation (AF) in 29.2% of the patients, valve replacement in 40.4%, cerebrovascular disease (CVD) in 10.1%, pulmonary thromboembolism (PTE) in 4.5%, deep vein thrombosis (DVT) in 6.7%, and other causes in 9%. Forty-five (51.7%) patients were found to have major hemorrhage and 44 (48.3%) had minor hemorrhage at emergency department admission. Among patients with major hemorrhage, 21 (46.6%) had intracranial hemorrhage, 20 (44.4%) had gastrointestinal system (GIS) hemorrhage, and 4 (8.9%) had a pericardial hemorrhage. Minor hemorrhage included hematuria in 18 (40.9%) patients and gingival hemorrhage in 26 (59.1%). Twenty-five percent of the patients died despite treatment (Table 1).

After admission, patients were evaluated, their laboratory tests were ordered, and treatment was started. The mean INR on admission was 9.48±5.8 (Table 1). VKA-induced bleeding was treated with 4-PCC (50 IU/kg) in 38.2% of patients and FFP in 61.8%. Vitamin K was administered to 44.9% of patients, but not to 55.1% of them. Patients treated with 4-PCC had a mean pre-treatment INR level of 8.68±5.51, a mean immediate post-treatment INR level of 1.91±0.93, and a mean 24th hour INR level of 2.44±1.31. Patients treated with FFP had a mean pre-treatment INR level of 9.98±5.96, a mean immediate
Discussion

Warfarin is the most widely used VKA drug. It acts by preventing the synthesis of vitamin K-dependent coagulation factors (factor 2, 7, 9, 10), with effective anticoagulation being determined by the therapeutic INR range [16]. 4-PCC and FFP are among the current treatments for the reversal of VKAs' effects in patients presenting with acute hemorrhage. Our study showed that 4-PCC reduced admission INR level to lower post-treatment levels compared with FFP among patients using VKAs and presenting with acute hemorrhage. Demeyere et al. reported that 4-PCC provided a quicker and more effective reversal of VKAs' effects compared with FFP in patients with a history of cardiopulmonary bypass [17]. Similarly, Hickey et al. detected that 4-PCC reversed the effect of VKAs more quickly and more effectively than FFP in the emergency department [18]. In addition to the treatment efficacy, the duration of the treatment also guides the clinician in the choice of treatment in patients with acute hemorrhage. Due to the need for blood post-treatment INR level of 3.03±1.53, and a mean 24th hour INR level of 2.88±2.10. An analysis of the change in INR levels showed that patients treated with FFP (10 mL/kg) had significantly lower post-treatment INR than the admission INR. Similarly, patients treated with 4-PCC also had a significantly lower post-treatment INR than the admission INR.

Comparison of post-treatment mortality rates showed a mortality rate of 36.4% among patients treated with FFP and only 14.4% in patients treated with 4-PCC, with the difference being statistically significant (p<0.001) (Table 1). In addition, comparison of the duration of administration revealed a significant difference between the 4-PCC treatment and the FFP treatment (Table 1).
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