



THROMBIN GENERATION ASSAY CHANGES AFTER PROTHROMBIN COMPLEX CONCENTRATE REVERSAL IN PATIENTS RECEIVING DIRECT ORAL ANTICOAGULANTS

Decharawee Nuntadee, Yupa Nakkinkun, Tussnem Binhama, Theera Ruchutakool
Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

INTRODUCTION

According to the efficacy, safety and convenience of administration, direct FXa inhibitors are increasingly used nowadays. However, problems with using of direct FXa inhibitors, especially major bleeding or pre-operative preparation are serious. Management of these complications remains challenge. Andexanet alfa, an antidote of direct FXa inhibitors, is a specific and effective reversal agent but is not universally available. Most of the clinical practice guidelines recommend the use of 4-factor prothrombin complex concentrates (4PCCs) as an alternative management strategy. Although 4PCCs have been confirmed to be effective hemostatic agents in these situations, the changes of thrombin generation after 4PCCs administration have not been extensively studied.

RESULTS

Fifteen patients with the median age of 77.87 ± 12.48 years were enrolled. Male was slightly predominant. Eighty percent of patients were non-valvular atrial fibrillation. Ten patients presented with major bleeding, and 5 patients required emergency operation. All patients achieved hemostatic control with 4PCCs. However, 6 patients (40%) received additional hemostatic supports as determined by their physicians. Plasma drug level at pre and post 4PCCs infusion were not different. Significant shortening of lag time by 1.15 minutes (95% CI -2.22 to -0.08; p value 0.036) and significant increase of endogenous thrombin potential (ETP) by 463.90 nM•minute (95% CI 204.95-722.84; p value 0.002) were detected. Other parameters of TGAs were not significantly different. Three patients died from complications unrelated to 4PCCs. No thrombotic complication was reported during hospitalization.

METHODS

Patients currently taking direct FXa inhibitors and having major bleeding or being prepared for an emergency surgery were enrolled. After informed consent, patients were given 50 units/kg of 4PCCs and had blood tests for drug level and thrombin generation assays (TGAs) at 15-30 minutes immediately before and after 4PCCs administration. Demographic information, clinical responses, volume of blood loss and mortality rate at 30 days were analyzed. Drug level and the changes of TGAs before and after 4PCCs administration were compared.

Table 1 Demographic characteristics of participants

Age (years)	77.87 ± 12.48
Indication	
AF	12 (80.0%)
VTE	3 (20.0%)
Types of DOACs	
Edoxaban	6 (40.0%)
Rivaroxaban	6 (40.0%)
Apixaban	3 (20.0%)
Creatinine clearance (ml/minute)	50.07 ± 25.83
Indication for PCC	
Pre-operative	5 (33.3%)
Bleeding	10 (66.7%)
Dose of PCC/kg	44.05±10.02

Table 2 Comparison of laboratory results before and after PCC administration after PCC administration

Blood tests	Before PCC	15-30 Minute after PCC	Mean difference (95%CI)		p-value [†]
	Mean ± SD	Mean ± SD			
Thrombin generation assay					
Lag time (min)	5.90 ± 2.58	4.75 ± 1.96	-1.15	(-2.22, -0.08)	0.036*
Time to peak (min)	24.55 ± 33.09	10.77 ± 4.87	-13.77	(-31.87, 4.32)	0.125
Peak height (nM)	89.87 ± 71.95	131.29 ± 80.45	41.41	(-3.70, 86.53)	0.069
ETP (nM•min)	976.17 ± 600.80	1440.07 ± 411.19	463.90	(204.95, 722.84)	0.002*
Coagulation times					
PT (seconds)	16.49 ± 3.49	15.17 ± 4.05	-1.31	(-3.69, 1.06)	0.253
APTT (seconds)	32.11 ± 7.43	33.50 ± 13.08	1.39	(-3.79, 6.58)	0.574

†Paired samples t-test, * Significant at p-value < 0.05

Conclusion

Conclusion: 4PCCs can shorten lag time and increase ETP, which well correlated with hemostatic control in patients receiving direct FXa inhibitors. Additional studies specifically targeting in an assessment of clinical endpoints and TGAs should be performed to further confirm these findings.

Reference

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