PROTHROMBIN COMPLEX CONCENTRATE FOR DOAC-ASSOCIATED INTRACEREBRAL HEMORRHAGE: FIRST CASE REPORT FROM VIETNAM

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Intracerebral hemorrhage (ICH) associated with direct oral anticoagulants (DOACs) is a life-threatening condition with a high risk of hematoma expansion. In settings where specific reversal agents such as andexanet alfa are unavailable, 4-factor prothrombin complex concentrate (4F-PCC) is commonly used as an alternative for urgent coagulation reversal. We report a 56-year-old man receiving rivaroxaban who presented with acute left thalamic intracerebral hemorrhage (baseline hematoma volume 3.6 mL). On admission, his international normalized ratio (INR) was 1.55 and anti-factor Xa level was 201.3 ng/mL. 4F-PCC was administered at a dose of 25 IU/kg (total 1,500 IU) at 5.7 hours after symptom onset (door-to-PCC time: 102 minutes). Thirty minutes after infusion, INR decreased to 1.28, with subsequent reduction in anti-Xa activity. Follow-up CT at 24 hours showed no hematoma expansion. No thromboembolic complications were observed. The patient achieved a favorable functional outcome (modified Rankin Scale score of 2) at discharge. This case illustrates the feasibility of 4F-PCC for early coagulation reversal in DOAC-associated ICH in a resource-limited setting. However, given the small hematoma volume and single-case design, the contribution of 4F-PCC to clinical outcome should be interpreted with caution.

Keywords: Prothrombin complex concentrate, direct oral anticoagulants, intracerebral hemorrhage.

I. INTRODUCTION

Intracerebral hemorrhage is one of the most severe forms of stroke, particularly in patients taking oral anticoagulants, including vitamin K antagonists and new-generation direct oral anticoagulants (DOACs). These cases often have poor outcomes, with reported mortality rates ranging from 24% to 67% in long-term observational studies.[1] New-generation direct oral anticoagulants (DOACs) are widely accepted due to their better safety profile compared to vitamin K antagonists (warfarin), reducing the risk of ICH by approximately 50%, but ICH is still a significant event with high mortality and disability rates. [2]

In the emergency treatment of intracerebral hemorrhage, the most important goal in the first few hours is to limit the progression of the hematoma. Current guidelines emphasize the role of targeted blood pressure control and correction of coagulation disorders as critical interventions that should be implemented as soon as possible, ideally within the first 60 minutes of hospital admission.[3,4]

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Except for dabigatran - a factor IIa anticoagulants which is currently available in Vietnam, other DOACs do not yet have widely available antidotes in clinical practice in many countries, including Vietnam. In this context, 4factor-prothrombin complex concentrate (4F-PCC) is often used as a compensatory way to correct coagulation disorders, aiming to improve hemostatic capacity through supplementation of vitamin K-dependent coagulation factors although it is not a specific antidote for any of DOACs. [5]frequently rapid clinical deterioration, and 30-days mortality of app 50%. This narrative review gives an overview of presentation and acute treatment of OAC-ICH. Oral anticoagulants do not cause ICH but lead to prolongation of bleeding and higher risk of hematoma expansion (HE [6]

However, 4F-PCC is not routinely available in some hospitals and emergency units in Vietnam, posing a major challenge in the emergency treatment of intracerebral hemorrhage associated with oral anticoagulants. This report aims to present a case of DOAC-associated intracerebral hemorrhage managed with prothrombin complex concentrate in a resource-limited setting

II. CASE PRESENTATION

A 56-year-old man presented with acute onset of right-sided hemiplegia.

His medical history included lower extremity Deep Vein Thrombosis with inferior vena cava filter placement 10 months prior, and pulmonary embolism 1 year prior. Given this history, the patient was being treated with rivaroxaban 20 mg/day, with the last dose was administered at 6:30 AM on the day of symptom onset

About 4 hours before admission, the patient was functioning and working normally while sudden-onset right hemiplegia occurred, accompanied by mild disorder of consciousness and vomiting. The patient was referred to our Stroke Center - Bach Mai Hospital by colleagues for emergency treatment.

Upon admission, the patient had a Glasgow Coma Scale (GCS) score of 13, blood pressure of 180/100 mmHg, pulse of 80 beats/minute, and SpO_2 of 98% on room air. Neurological examination revealed right-sided hemiplegia, with a NIHSS score of 10.

The patient underwent emergency laboratory tests at 14:45, including a complete blood count, serum biochemistry, coagulation tests, and anti-Xa activity quantification, and underwent multislice CT with cerebral angiography (MSCT). The CT images showed parenchymal hemorrhage in the left thalamic-brainstem region, with an estimated hematoma volume of 3.6 mL. No spot sign was detected, and there were no sign suggestive of active intracerebral hemorrhage at the time of the scan.

The patient was managed according to the institutional CODE ICH protocol, including controlling blood pressure to a low target of 130-150 mmHg with intravenous nicardipine. The blood pressure target was achieved after 30 minutes with a nicardipine dose of 4 mg/hour and maintained stable for the first 60 minutes after admission. Simultaneously, the patient's coagulation disorder was corrected and other standard resuscitation measures were applied.

The results of the patient's paraclinical tests are presented in detail in Table 1.

Table 1. Paraclinical characteristics of the patients

	Before 4F-PCC infusion	After 4F-PCC infusion	After 48 hours
PT/INR	52% / 1.55	68% / 1.28	82% /1.1
PLT (G/L)	259	-	278
Fibrinogen (g/dL)	3.28	3.30	3.28
Anti-Xa (ng/ml)	201.3	170	52.4
Creatinin (µmol/L)	68	-	74
GFR (ml/ph/1,73 m2	102		98

PT: prothrombin time, INR: international normal ratio, PLT: platelet count, anti-Xa: anti-Xa factor specific for rivaroxaban, eGFR: estimated glomerular filtration rate

The patient underwent a multidisciplinary consultation involving stroke specialists, clinical pharmacists, and cardiologists. After careful evaluation and informed consent obtained from the patient's family, 4-factor prothrombin complex concentrate (4F-PCC) was administered for reversal of coagulopathy at a dose of 25 IU/kg (total dose: 1,500 IU). 4F-PCC was administered 5.7 hours after symptom onset, corresponding to 102 minutes after hospital admission. The "door-to-PCC" time was 102 minutes, whereas the time from prescription to drug administration was 12 minutes.

30 minutes post-PCC infusion, coagulation tests showed improvement in the PT/INR index, reaching the target goal with an INR of 1.28. No acute thromboembolic event was recorded during or immediately after the infusion

At 24 hours post-symptom onset, a follow-up CT scan of the brain was performed, revealing a stable hematoma with no sign of expansion or progression compared to the baseline imaging.

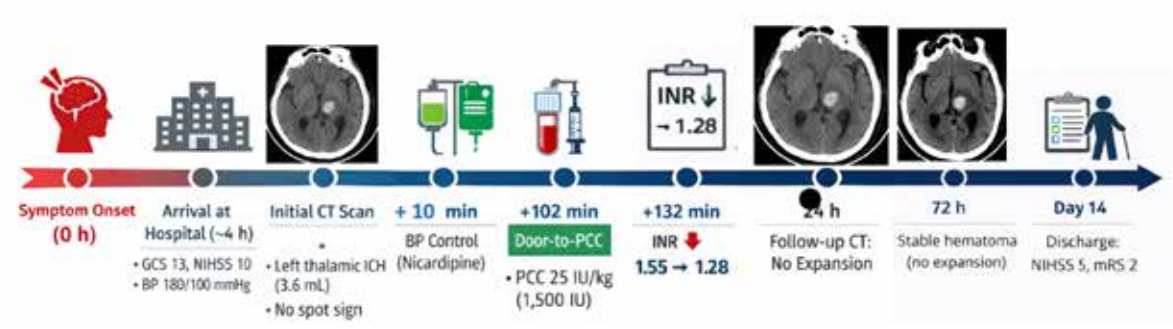

Figure 1. Clinical timeline of hemorrhage management

Evaluations to rule out thromboembolic complications following 4F-PCC administration were performed in detail, including lower limb venous duplex ultrasound, echocardiography, CT pulmonary angiography and no evidence of new thrombus formation was found. Blood pressure control, early rehabilitation initiated after 48 hours, the use of compression stockings, nutritional support, and close clinical monitoring for hematoma expansion and post-PCC complications were strictly maintained during the treatment course and fortunately,

no adverse event occurred.The patient was discharged after a total of 14 admission days, with no mental status change, Glasgow score of 15, NIHSS score of 5 and modified Rankinscale score of 2 and muscle strength graded 4/5 in extremities. A follow-up visit was scheduled, and a plan was established to resume anticoagulation therapy after 8-12 weeks. Written informed consent was obtained from the patient for publication of this case report.

III. DISCUSSION

Intracerebral hemorrhage associated with direct oral anticoagulants (DOAC-ICH) remains a major clinical challenge due to the high risk of early hematoma expansion, which is a key determinant of mortality and functional outcome. Early reversal of anticoagulation is therefore considered a cornerstone of acute management. While specific reversal agents such as andexanet alfa are recommended for factor Xa inhibitors, their limited availability and high cost restrict their use in many low- and middle-income countries, including Vietnam.[6]

In this context, 4-factor prothrombin complex concentrate (4F-PCC) is frequently used as an alternative strategy for coagulation reversal. Although 4F-PCC does not directly neutralize factor Xa inhibitors, it enhances thrombin generation through supplementation of vitamin K-dependent clotting factors. Current international guidelines suggest considering 4F-PCC at doses of 25-50 IU/kg in DOAC-associated major bleeding when specific antidotes are not available. In our case, a low dose strategy was selected, balancing hemostatic benefit and thromboembolic risk.[5,7,8]

The timing of anticoagulation reversal is increasingly recognized as a critical factor in DOAC-ICH. Recent observational studies have suggested that shorter time to reversal is associated with reduced hematoma expansion and improved outcomes. In our patient, 4F-PCC was administered 102 minutes after hospital admission, reflecting the feasibility of relatively early intervention in a real-world clinical setting. However, this interval remains longer than the ideal targets reported in high-resource settings, highlighting opportunities for further optimization of in-hospital workflows.[9,3]

Monitoring of anticoagulant activity remains another important but challenging aspect. Anti-factor Xa activity in our patient was markedly elevated on admission and showed a decreasing trend following 4F-PCC administration. Although no universally accepted threshold exists to guide reversal therapy, elevated anti-Xa levels may support the presence of clinically relevant anticoagulant effect. Nevertheless, the role of serial anti-Xa monitoring in guiding treatment decisions remains uncertain and requires further investigation.[10]

Importantly, the favorable clinical and radiological outcomes observed in this case should be interpreted with caution. The baseline hematoma volume was relatively small (3.6 mL), which is independently associated with a lower risk of expansion and better prognosis. In addition, early and effective blood pressure control may have contributed significantly to hematoma stability. Therefore, the absence of hematoma expansion cannot be solely attributed to 4F-PCC administration. The safety of 4F-PCC, particularly the risk of thromboembolic complications, remains a concern. 4F-PCC increases circulating levels of clotting factors and may promote a prothrombotic state, especially in patients with a prior history of thrombosis. In our case, no thromboembolic event was detected during hospitalization; however, the short follow-

up period limits the assessment of delayed complications. Careful patient selection and close monitoring are therefore essential when using 4F-PCC in this setting.[11]

This case highlights several practical considerations in the management of DOAC-associated ICH in resource-limited environments: (1) 4F-PCC may serve as a feasible alternative when specific antidotes are unavailable; (2) rapid treatment initiation is achievable but requires optimized institutional protocols; and (3) clinical decision-making must balance the risks of ongoing bleeding and thrombosis on an individual basis

However, this clinical case has several limitations. Firstly, the door-to-PCC time was relatively delayed compared to international reports, reflecting the early stages of implementing 4F-PCC protocols at the facility.[12] Secondly, 4F-PCC only serves as a compensatory correction of coagulopathy in the absence of specific antidotes, therefore, patients still require periodic monitoring of coagulation profiles and anti-Xa levels.[3] Additionally, since this is a single case without a control group, involving a small initial hematoma volume and a limited follow-up period, it is not possible to generalize the efficacy or fully assess the risk of late thromboembolism following 4F-PCC use. Finally, the independent role of early blood pressure control in hematoma stabilization cannot be entirely ruled out.

IV. CONCLUSION

4-factor prothrombin complex concentrate (4F-PCC) may be a feasible option for anticoagulation reversal in DOAC-associated intracerebral hemorrhage, particularly in resource-limited settings. However, conclusions regarding its effectiveness should be interpreted with caution given the single-case design and the small baseline hematoma volume. This first reported case in Vietnam may assist toward the development of national protocols and highlights the need for local registries and future prospective studies.

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