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Outcome following intracranial hemorrhage associated with novel oral anticoagulants

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ABSTRACT

The emergence of dabigatran, rivaroxaban and apixaban has changed the approach to anticoagulation for patients worldwide. Continued approval of novel oral anticoagulants (NOAC) for non-valvular atrial fibrillation and venous thromboembolism will result in increasing use of these medications over warfarin. Morbidity and mortality of anticoagulant related intracranial hemorrhage (ICH) is relatively high and there is concern that outcomes may be worse with NOAC as there is a lack of specific antidotes for these agents with a greater risk for hematoma expansion. Unfortunately, the evidence supporting effective reversal strategies is lacking. Therefore, to gain further insight into the outcome after the management of NOAC related ICH, we present our experience with two patients with NOAC-induced ICH.

1. Introduction

Anticoagulants are frequently used for various indications, including prevention of venous thromboembolism after orthopedic surgery, treatment of acute venous thromboembolism, and prevention of arterial thromboembolism in atrial fibrillation [1–3]. Warfarin has been the most commonly prescribed anticoagulant to treat and prevent thrombosis for many decades. Three novel oral anticoagulants (NOAC), dabigatran, rivaroxaban and apixaban, have recently been approved by the USA Food and Drug Administration for the prevention of arterial thromboembolic events in non-valvular atrial fibrillation as an alternative to warfarin [4–6]. As the use of these NOAC increases over time, neurosurgeons will be confronted with managing patients receiving these medications more often, secondary to the risk of development of ICH while on these NOAC [7]. We report our experience with two patients who sustained ICH while on NOAC along with a review of the literature.

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2. Case Description

2.1. Patient 1

An 83-old-man presented with acute onset of weakness for 1 day. CT scan of the head revealed an ICH involving the left basal ganglia (Fig. 1). Past medical history was significant for well controlled hypertension and non-valvular atrial fibrillation for which he was receiving rivaroxaban 20 mg daily, the last dose being taken about 12 hours prior to the onset of symptoms. Neurological examination at presentation was within normal limits except for a subtle right sided pronator drift. Laboratory analysis showed serum creatinine, prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (PTT) to be within normal limits. He was immediately reversed with factor XIII inhibitor bypassing activity (FEIBA) 30 international units/kg in consultation with a hematologist and monitored in the neuroscience intensive care unit. Repeat CT scan performed 24 hours after admission showed no expansion in the size of the hematoma with stable neurological exam. He was subsequently discharged home and was doing well at last follow-up at 3 months.

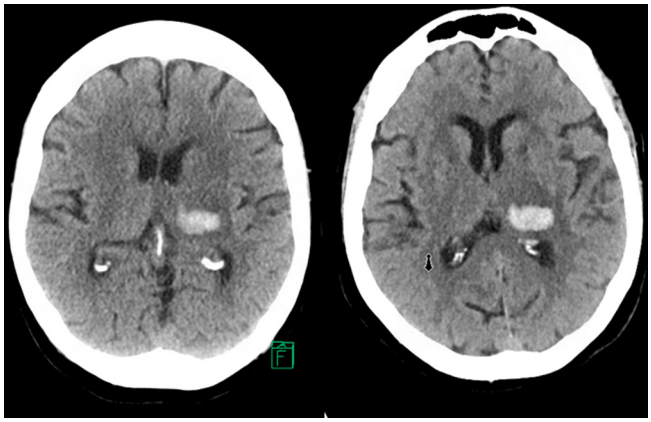

Fig. 1. Axial non-contrast CT scan of the head showing an acute hemorrhage in the left thalamus measuring 2 × 1 cm in axial section with no significant mass effect or midline shift (left). Repeat CT scan done after 24 hours demonstrating stable hemorrhage (right).

2.2. Patient 2

An 80-year-old man with significant past medical history of deep vein thrombosis on dabigatran 150 mg every 12 hours presented to an outside hospital after 2 days of altered mental status and right sided weakness. He was taking dabigatran as prescribed with the most recent dose taken the morning of presentation. CT scan of the head showed a left sided acute on chronic subdural hematoma (SDH) with significant mass effect and midline shift (Fig. 2). Laboratory analysis showed serum creatinine within normal limits with PT, INR and APTT on admission being 14.8 seconds (normal range 9.5–13.2 seconds), 1.48 (normal range 0.8–1.2), and 45.8 seconds (normal range 23–33 seconds) respectively. Surgical treatment was deemed appropriate, but as he recently took dabigatran, it was deferred considering his good neurological examination apart from minimal right pronator drift. The family was informed about the risk and benefits and a collective decision to delay the surgery (reserving it for acute deterioration) was made. He was closely monitored in the neuroscience intensive care unit with repeat CT scan of the head performed at 6 and 24 hours after admission showing stable SDH (Fig. 2) with no worsening of neurological examination. Since he was more than 96 hours out from his last dose of dabigatran and his PT/INR and PTT normalized, surgery was performed with successful removal of the SDH through a mini craniotomy. Excessive bleeding was not encountered during surgery and hemostasis was achieved without difficulty. Throughout the inpatient stay, he did not experience neurological deterioration which was attributable to rebleeding as subsequent post-operative CT scans showed good decompression with resolution of the mass effect and midline shift. However, he experienced a prolonged post-operative recovery and required a tracheostomy as he could not be weaned off the ventilator. He was finally transferred to a nursing home.

3. Discussion

Neurosurgeons and neurointensivists are frequently involved in the management of anticoagulant related ICH. There are pharmacologic strategies to reverse the effect of traditional anticoagulants such as warfarin, unfractionated heparin and low molecular weight heparin, which may improve the overall outcome by reducing hematoma expansion, related mass effect and midline shift [1,2,8]. This may involve reversal with fresh frozen plasma, phytonadione, prothrombin complex concentrates (PCC), and recombinant activated factor VII (rVIIa). Regardless of the availability of reversal agents and their efficacy in reversing the anticoagulation effect of warfarin, reversal of anticoagulation may not always translate to good clinical outcome which is probably related to the severity of initial hemorrhage [9]. Likewise, even though platelets are often administered in patients who sustain ICH on antiplatelet agents such as aspirin and clopidogrel, there is no true antidote for these agents either. As compared to warfarin, where there are well defined reversal strategies for preventing expansion of ICH in the event of bleeding, pharmacologic strategies to reverse NOAC in cases of life threatening hemorrhage are lacking and experience is limited mostly to animal studies, *in vitro* studies and case reports [7,10–21]. In addition, coagulation assays used to confirm the anticoagulant effect of NOAC are limited to clinical studies and not commercially available at this time [22]. This makes it very difficult to confirm the effect of the various pharmacologic agents used to reverse these agents in clinical practice.

Upon our review of all the reported cases of NOAC associated ICH at the time of writing, (total 18 patients, including this study) there were seven deaths leading to an overall mortality rate of 39% (7/18) [10–12,15,16,19–21]. Previous reports have focused mainly on dabigatran associated hemorrhages. The management of these patients who sustained ICH while on dabigatran varied among institutions and reflects the problems associated with incomplete dabigatran reversal (Table 1). Even though various pharmacologic agents such as PCC and rVIIa have been administered to patients who sustained a dabigatran associated ICH, it is unknown whether

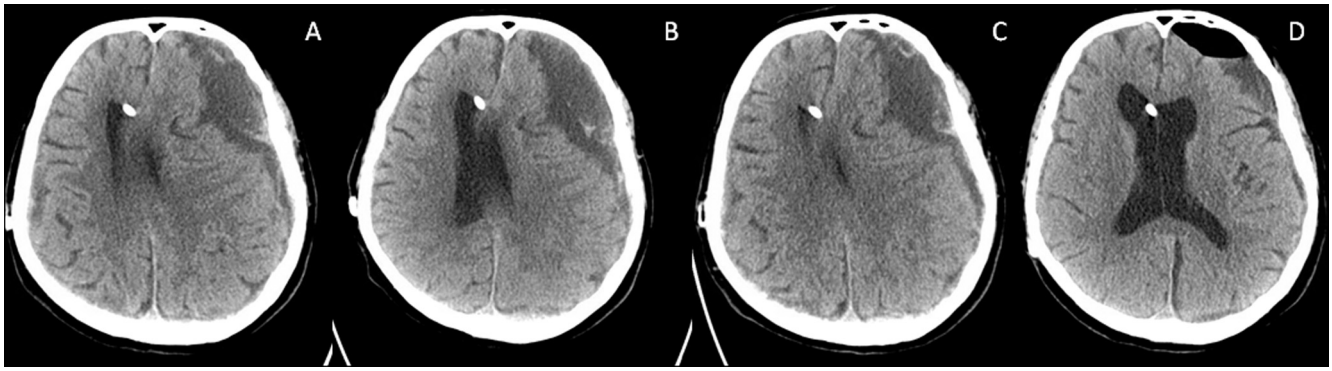

Fig. 2. Axial non-contrast CT scan of the head demonstrating left sided acute on chronic subdural hematoma, with significant mass effect and midline shift (A). Also seen is the ventricular end of the shunt from prior surgery. Repeat axial CT scan performed at 6 hours (B) and 24 hours (C) showing no increase in the size of the hematoma. Post-operative axial CT scan of the head (D) demonstrating good decompression with improvement in mass effect and midline shift and no hemorrhagic complication.