Resolution of Internal Carotid Arterial Thrombus by the Thrombolytic Action of Dabigatran

A first case report

Hisanao Akiyama, MD, PhD, Masashi Hoshino, MD, Takahiro Shimizu, MD, PhD, and Yasuhiro Hasegawa, MD, PhD

Abstract: Non-vitamin K antagonist oral anticoagulants (NOACs) have been reported to cause resolution of intracardiac thrombus, but there have been no reported cases of internal carotid arterial thrombus resolution.

We report a case of a 76-year-old man in whom an internal carotid arterial thrombus resolved after administration of the NOAC dabigatran at a dose of 110 mg twice daily.

This is the first reported case of carotid arterial thrombus resolution after oral intake of NOAC (direct thrombin and factor Xa inhibitors), to the best of our knowledge.

We conclude that this case had major clinical significance because it might represent one of the multiple effects of NOACs.

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INTRODUCTION

Recently, there have been increasing opportunities to use non-vitamin K antagonist oral anticoagulants (NOACs) instead of warfarin in the prevention of cardiological cerebral embolism due to nonvalvular atrial fibrillation (NVAF). Several randomized controlled trials have shown that these NOACs are superior to warfarin in the prevention of cardiological cerebral embolism and that there are fewer concomitant intracranial hemorrhages.

During atrial fibrillation, thrombus tends to form readily because there is excessive promotion of blood coagulation. This thrombogenesis is suppressed by these NOACs, which inhibit thrombin or factor Xa and prevent the formation of new intracardiac thrombus. Recently, there have also been a number of reports indicating that existing intracardiac thrombus also resolve, despite the fact that an obvious mechanism has not yet been elucidated. Although many effects continue to be observed, there have been no reports regarding the resolution of internal carotid arterial thrombus.

Here, we report a case in which resolution of an extracardiac thrombus within the internal carotid artery was achieved through oral administration of the NOAC dabigatran.

Case Report

A 76-year-old man was taking oral warfarin for chronic NVAF. He experienced ataxia and dysarthria on December 16, 2010, and was admitted to our hospital with cardiogenic cerebral embolism affecting the right superior cerebellar artery region. Because prothrombin time-international normalized ratio (PT-INR) was 1.20 on admission, the dose of warfarin was increased while also administering unfractionated heparin intravenously. On January 6, 2011, the patient was discharged without assistance. Fluxuation of the PT-INR subsequently continued while the patient was treated on an outpatient basis. On March 13, 2012, the patient experienced dysarthria and right central facial nerve paralysis, and he was admitted until March 23 for cardiogenic cerebral embolism affecting the area from the left insular cortex to the cortical and subcortical regions in the precentral gyrus. PT-INR on admission was 1.25, indicating a subtherapeutic INR. When we investigated the source of the embolus, no thrombus was observed in the carotid arteries or inside the heart. After the dose of warfarin was adjusted while administering unfractionated heparin intravenously, the patient was discharged without assistance. Continued fluctuation of PT-INR levels was noted in the blood tests performed at the outpatients department after discharge. We switched the patient from warfarin to dabigatran 110 mg twice daily because of low creatinine clearance on May 15, 2012, and have not observed any new cerebrovascular events to date.

In early 2015, pharyngeal obstruction was observed, and upper gastrointestinal endoscopy revealed type I squamous cell carcinoma of the thoracic esophagus (T3N1M0 stage III). The patient was admitted to the Department of Gastrointestinal Surgery for workup to decide the treatment strategy on March 9. Carotid artery ultrasound unexpectedly showed thrombus formation at the right internal carotid artery, which was performed to evaluate the metastasis in the cervical lymph node on March 9, and it was repeated to reconfirm the existence of the thrombus on March 13 (Figure 1A, B). A request for treatment was made to the Department of Neurology approximately 10 days later on March 24. Neurological examination on the same day showed only the already-known ataxic speech and mild truncal ataxia. Atrial fibrillation was also observed on electrocardiogram. Prior to admission, oral dabigatran intake was...
irregular, and the drug was taken only approximately 60% to 70% of the time due to obstruction caused by the esophageal carcinoma. After admission, there was a request for treatment to be administered orally at regular times. When we repeated the carotid artery ultrasound on the same day, the thrombus at the same site had disappeared and only "spontaneous echo contrast (SEC)" was observed (Figure 1C). Black blood magnetic resonance imaging at the carotid artery on March 26 (Figure 2) revealed a hyperintensity, indicating the presence of an unstable plaque, on T1- and T2-weighted images, but no thrombus at this site. On April 23, cranial magnetic resonance revealed that there were no new cerebral infarctions and no occlusions of the intracranial vessels (Figure 3). We subsequently repeated the carotid artery ultrasound on June 30 (Figure 4) and did not observe thrombus within the right internal carotid artery; similar to the previous time, we only observed mild SEC. During the admission, he did not have any medical treatment such as chemotherapy or radiation. In blood tests of the coagulation-fibrinolytic system, activated partial thromboplastin time was 35.7 (control: 30.0) s, PT-INR was 1.15, and D-dimer was <0.3 (normal range 0–0.5) mg/mL on March 9 when oral dabigatran intake had been inadequate. Tests on July 22, after regular dabigatran intake, revealed an activated partial thromboplastin time of 49.4 (control: 30.2) s, a PT-INR of 1.48, D-dimer <0.3 µg/mL, antithrombin of 77 (normal range 75–125)%, soluble fibrin monomer complex value of 1.7 (normal range 0–6.1) µg/mL, and a plasminogen activator inhibitor-1 of 61 (normal range ≤50) ng/mL.

**DISCUSSION**

In this case, we administered the NOAC dabigatran to prevent recurrence of cardiogenic cerebral embolism due to NVAF, but a thrombus formed in the internal carotid artery due to irregular oral intake of the drug. After regular intake was ensured, the thrombus disappeared. To our knowledge, this is the first report of such an event, and we believe this report is of clinical significance as it might represent one of the many effects of NOACs.

Dabigatran acts as a direct thrombin inhibitor. It directly and reversibly binds to the active sites of initial and free thrombin, inhibiting their activation.\(^{17}\) The result is suppressed conversion of soluble fibrinogen into fibrin monomers or finally into stabilizing fibrin by the fibrin stabilizing factor, which is coagulation factor XIII activated by thrombin. In addition, dabigatran also binds to the active site of fibrin-bound thrombin. By doing so, it inhibits the extension of the thrombus. Nevertheless, it is mainly known for its inhibitory effects on new

![Figure 1](image-url). Carotid artery ultrasound on admission (A), the 5th day after admission (B), and the 16th day after admission (C). The carotid artery ultrasound performed at the time of admission and on the 5th day of hospital stay showed a thrombus at the right internal carotid artery on both days. Ten days later, a repeat ultrasound at the same site showed that the thrombus had disappeared, leaving only “spontaneous echo contrast.” CCA = common carotid artery, ICA = internal carotid artery, Rt = right.
FIGURE 2. Black blood MR imaging at the carotid artery after disappearance of cervical thrombus. We observed a hyperintensity, indicating the presence of an unstable plaque, at the right internal carotid artery on T1- and T2-weighted images, but there was no thrombus. ICA = internal carotid artery, MR = magnetic resonance, MRA = magnetic resonance angiography, Rt = right, T1WI = T1 weighted image, T2WI = T2 weighted image.

FIGURE 3. Cranial MR imaging and angiography after disappearance of intracarotid artery thrombus. No new cerebral infarctions and no occlusions of the intracranial vessels on MR images and angiography. DWI = diffusion weighted image, FLAIR = fluid attenuated inversion recovery, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, Rt = right.
thrombus formation and is not known to cause the resolution of existing thrombus.

However, in 2012, Vidal and Vanerio first reported treatment of a 59-year-old woman with an 8 × 8 cm thrombus in the left atrial appendage with dabigatran 150 mg twice daily, resulting in thrombus resolution in 6 to 7 weeks and no new cerebral embolism. There have been some reports of similar intracardiac thrombus resolution after the administration of dabigatran or the Xa inhibitors rivaroxaban or apixaban. Furthermore, differences were observed in thrombus resolution at different doses of dabigatran. Tabata et al reported that resolution of intracardiac thrombus after administration of dabigatran 110 mg twice daily was insufficient. Very few of these reports clearly mention the resolution mechanism. Of those that did, Kaku described that dabigatran induced endogenous fibrinolysis, while Nagamoto et al reported dabigatran had thrombolytic action on acute preexisting intracardiac thrombus. Regarding rivaroxaban, Kato et al presumed that there was promotion of fibrinolysis due to a peak and trough period, and Takasugi et al reported that rivaroxaban caused a looser clot to form that is more sensitive to fibrinolytic enzyme by decreasing thrombin production. In our case, we speculate that a new thrombus formed on the unstable plaque that was originally present at the site of onset in the right internal carotid artery when oral intake of dabigatran was insufficient, and after admission, oral intake of dabigatran became regular and there was resolution of the new thrombus by a mechanism similar to that of resolution of intracardiac thrombus in previous reports.

There are several issues in this case. First, it is possible that the presence of esophageal carcinoma affected the coagulation-fibrinolytic system when the thrombus developed or resolved in the internal carotid artery. Second, when the oral intake of dabigatran was irregular, the D-dimer value, which indicates stabilizing fibrin thrombus formation, was normal during development of the internal carotid thrombus. We speculate that the reason was the lack of conversion of fibrinogen into stabilizing fibrin because dabigatran suppressed the activation of coagulation factor XIII while it was being administered with incomplete dosing. In other words, the thrombus was easily degraded by plasmin because it was a looser thrombus in a soluble fibrin state, and so it did not lead to an elevated D-dimer value. Third, there was no pathological verification of the thrombus that formed in the internal carotid artery. Regarding the component of that thrombus, there is usually formation of a platelet-rich white thrombus due to the high flow velocity in the arteries, but there are some reports of the presence of fibrin-rich red thrombus. In our case, as we saw SEC in both carotid artery ultrasound investigations, even though there was a site where the flow velocity was high and there was no severe stenosis at this site, it was obvious that there was regional blood stasis or low-velocity blood flow. For this reason, we considered the possible mechanism of internal carotid arterial thrombus formation.
resolution by the direct thrombin inhibitor as follows: the rupture of an existing, unstable plaque caused activation of the coagulation system at this site, formation of a red thrombus, and then resolution of the red thrombus, which is the same process as in the resolution of an intracardiac thrombus.

In conclusion, we reported a case of internal carotid arterial thrombus resolution due to the administration of oral dabigatran. This is the first reported case to the best of our knowledge. This case has major clinical significance because it might represent one of the multiple effects of NOACs. Going forward, we will need to investigate more cases and perform large-scale studies.

CONSENT
The patient or their next of kin gave written informed consent for publication of this report.

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