



Case Report

Intracranial hemorrhage associated with direct oral anticoagulant after clipping for an unruptured cerebral aneurysm: A report of two cases

Takahiro Koji, Yoshitaka Kubo, Yoshiyasu Matsumoto, Yosuke Akamatsu, Kohei Chida, Hiroshi Kashimura, Kuniaki Ogasawara

Department of Neurosurgery, Iwate Medical University, Yahaba, Iwate, Japan.

E-mail: Takahiro Koji - thkoji@iwate-med.ac.jp; *Yoshitaka Kubo - yokubo@iwate-med.ac.jp; Yoshiyasu Matsumoto - yoshiyasu.matsumoto@gmail.com; Yosuke Akamatsu - akamatsu@iwate-med.ac.jp; Kohei Chida - kchida@iwate-med.ac.jp; Hiroshi Kashimura - hkashimura@icloud.com; Kuniaki Ogasawara - kuogasa@iwate-med.ac.jp

*Corresponding author:

Yoshitaka Kubo,
Department of Neurosurgery,
Iwate Medical University,
Yahaba, Iwate, Japan.

yokubo@iwate-med.ac.jp

Received : 09 December 2021

Accepted : 03 March 2022

Published : 25 March 2022

DOI

10.25259/SNI_1223_2021

Quick Response Code:



ABSTRACT

Background: Two cases of patients who developed intracranial hemorrhage associated with direct oral anticoagulant (DOAC) use after clipping of an unruptured cerebral aneurysm (uAN) are presented. These cases will help neurosurgeons assess the risks of patients with atrial fibrillation or deep venous thrombosis receiving DOACs who require craniotomy.

Case Description: Case 1 was a 65-year-old man on apixaban 10 mg/day who underwent clipping for a left middle cerebral artery uAN. Apixaban was discontinued 72 h before surgery. During surgery, a thin and pial artery bled slightly at 1 point of the frontal lobe, and hemostasis was easily achieved. Computed tomography (CT) 19 h after surgery showed no evidence of intracranial hemorrhage. He was treated with a heparin-apixaban bridge from 29 h to 41 h after surgery. CT showed a left subarachnoid hematoma 24 h later. Case 2 was a 73-year-old woman on dabigatran 110 mg/day who underwent clipping for a right MCA uAN. Dabigatran was discontinued 48 h before surgery. During surgery, a thin and pial artery bled slightly at 2 points of the temporal lobe, and hemostasis was easily achieved. CT 19 h after surgery showed no evidence of intracranial hemorrhage. Dabigatran (110 mg/day) was restarted 29 h after surgery. CT then showed a right subarachnoid hematoma 94 h later, and dabigatran was discontinued, and it was then restarted 38 h later. However, 31 h later, CT showed an additional slight subarachnoid hemorrhage. Finally, she developed a right chronic subdural hematoma.

Conclusion: In patients undergoing neurosurgical procedures, discontinuation of DOACs should be individualized based on neurosurgical bleeding risk and patient renal function. Restarting of DOACs could be considered after at least 48 h when hemostasis has been achieved. Bridging of DOACs cannot be recommended.

Keywords: Cerebral aneurysm, Clipping, Direct oral anticoagulant, Intracranial hemorrhage

INTRODUCTION

Several previous studies including autopsy reports have demonstrated that the formation and growth of unruptured cerebral aneurysms that might result in subarachnoid hemorrhage increase with advancing age.^[11,12,15] On the other hand, the prevalence of atrial fibrillation (Af), which could cause cerebral embolism resulting in death or severe neurological deficits, also increases with aging.^[2,20] Direct oral anticoagulants (DOACs) are increasingly being used as an alternative to Vitamin K antagonists for the prevention of cerebral embolism from Af, and they have shown

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lower rates of intracranial hemorrhage. However, little evidence is available regarding the management of patients treated with DOACs who require cranial surgery including cerebral aneurysm clipping. Therefore, their management during the perioperative period has become a frequent dilemma for neurosurgeons.

Two cases of patients who underwent craniotomy for surgical clipping of unruptured cerebral aneurysms and developed intracranial hemorrhage associated with DOACs are presented. These cases will help neurosurgeons assess the risks of patients with Af or deep venous thrombosis receiving DOACs who require craniotomy.

CASE DESCRIPTION

Case 1

A 65-year-old man was on apixaban 10 mg/day as a DOAC for embolic cerebral infarction in the left occipital lobe and cerebellum associated with paroxysmal nonvalvular Af. He has a CHADS₂-VASc score^[14] of 3, implying an annual stroke risk of 3.2%. He underwent clipping surgery for an unruptured aneurysm of the left middle cerebral artery. Preoperative investigations showed creatinine clearance of 85.2 ml/min/1.73 m². Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were 15.7 s (normal range: 10.8–12.6 s) and 34.7 s (normal range: 26.2–36.1 s), respectively. Apixaban was discontinued 72 h before surgery, and heparin 12,000 units/day was given intravenously until 6 h before surgery. PT and aPTT were 13.7 and 31.2 s, respectively, 4 h before surgery. During surgery, a thin and pial artery bled slightly at 1 point of the left frontal lobe [Figure 1a], and hemostasis was easily achieved using cotton without the use of the gelatin sponge and/or oxidized regenerated cellulose. PT and aPTT immediately after surgery were 12.2 s and 29.2 s, respectively. Computed tomography (CT) immediately and 19 h after surgery showed no evidence of intracranial hemorrhage [Figure 1b]. He received heparin 12,000 units/day intravenously, and 10 h later, apixaban 5 mg/day was also started. Furthermore, 12 h later, apixaban 10 mg/day was given. The so-called heparin-DOAC bridge was continued for 12 h and heparin administration was then stopped. However, 24 h later, he suffered sudden onset of aphasia, and CT showed a subarachnoid hemorrhage in the left Sylvian fissure [Figure 1c]. CT angiography showed disappearance of the aneurysm. PT and aPTT were 14.4 s and 32.1 s, respectively. After discontinuation of apixaban, his symptom gradually resolved. Ten days later, the DOAC was restarted; follow-up CT subsequently showed no additional increase of the hematoma [Figure 1d], and magnetic resonance imaging (MRI) showed no new cerebral infarction. He was discharged home 39 days after surgical clipping. The clinical time course of Case 1 is shown in [Figure 2].

Case 2

A 73-year-old woman was on dabigatran 110 mg/day as a DOAC for embolic cerebral infarction in the right frontal lobe with paroxysmal nonvalvular Af. She had a CHADS₂-VASc score^[14] of 4, implying an annual stroke risk of 4%. She underwent clipping surgery for an unruptured aneurysm of the right middle cerebral artery. Preoperative investigations showed a creatinine clearance of 58.2 ml/min/1.73 m². PT and aPTT were 15.7 s and 59.3 s, respectively. Dabigatran was discontinued 48 h before surgery. PT and aPTT were 14.9 s and 39.0 s, respectively, 4 h before surgery. During surgery, a thin and pial artery bled slightly at 2 points of the temporal lobe [Figure 3a], and hemostasis was easily achieved using cotton without the use of the gelatin sponge and/or oxidized regenerated cellulose. PT and aPTT immediately after surgery were 13.9 s and 31.7 s, respectively. CT immediately and 19 h after surgery showed no evidence of intracranial hemorrhage [Figure 3b]. 10 h later, dabigatran (110 mg/day) was given. However, 94 h later, she suffered a sudden headache, CT showed a subarachnoid hemorrhage in the right Sylvian fissure [Figure 3c], and dabigatran was discontinued. CT angiography showed the disappearance of the aneurysm. Dabigatran was restarted 38 h later. However, 31 h later, she developed sudden headache, CT showed an additional slight subarachnoid hemorrhage, and dabigatran was discontinued. Dabigatran was restarted 240 h later, and she was discharged home 18 days after surgical clipping. However, 18 days later (864 h after surgery), she developed a right chronic subdural hematoma [Figure 3d] and underwent irrigation surgery. Dabigatran was restarted 21 days after irrigation. Follow-up CT subsequently showed no additional increase of the hematoma and no new cerebral infarction was seen on MRI. The clinical time course of Case 2 is shown in [Figure 4].

DISCUSSION

Although the present two patients underwent gentle surgical clipping for unruptured cerebral aneurysms, intracranial hemorrhage developed. According to a meta-analysis^[1] of procedural clinical complications in surgical clipping of unruptured cerebral aneurysms, they were increased in patients on anticoagulation therapy (pooled OR, 6.36). In another study,^[6] the postoperative bleeding rate in patients undergoing cranial surgery with a DOAC was 13.3% ($n = 4$ of 13), including burr hole surgery for chronic subdural hematoma in two patients, biopsy for brain tumor in one patient, and decompressive craniotomy for trauma, and a shorter preoperative discontinuation time seemed to have a significant effect on the bleeding rate. However, invasive techniques such as the trans-Sylvian approach for cerebral aneurysms have not been described.^[6] In the present Cases 1 and 2, intracranial hemorrhage developed 68 h and 124 h after surgery, respectively. Basali *et al.* found that blood

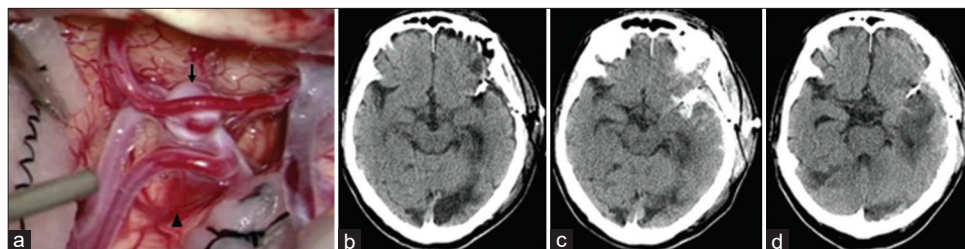


Figure 1: Case 1 (a) During surgical clipping for an aneurysm (arrow) of the left middle cerebral artery, a thin and pial artery bleeds slightly at 1 point of the left frontal lobe (arrowheads), and hemostasis is easily achieved using cotton. (b) Computed tomography (CT) 19 h after surgery shows no evidence of intracranial hemorrhage. (c) CT 36 h after restarting apixaban (24 h after discontinuing the heparin-DOAC bridge) shows subarachnoid hemorrhage in the left Sylvian fissure. (d) CT 240 h after surgery shows no additional increase of the hematoma.

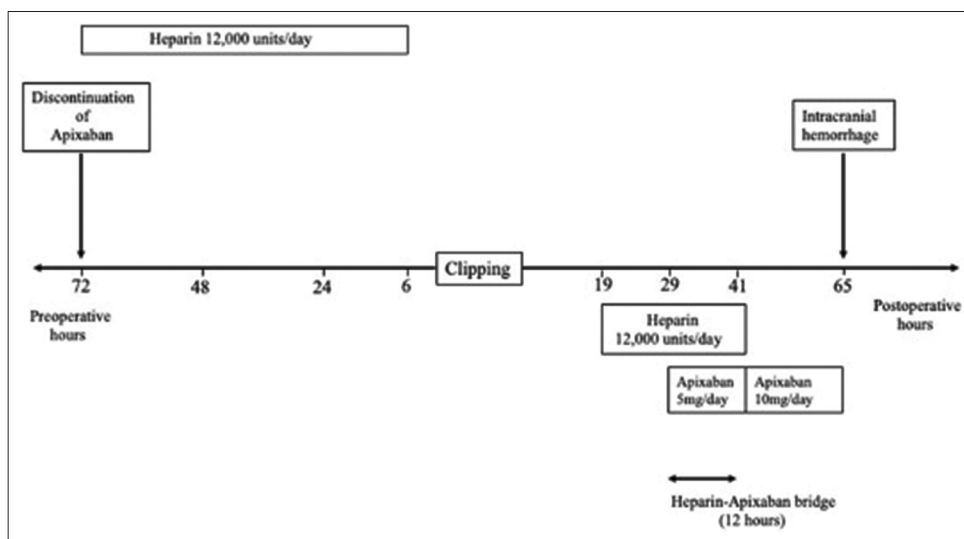


Figure 2: The clinical time course of Case 1.

pressures greater than 160/90 mmHg in the perioperative period were significantly associated with postoperative hemorrhage.^[4] Both of the present cases had blood pressure levels within 145/80 mmHg throughout the entire perioperative period (systolic/diastolic blood pressure; Case 1: 106–142/65–77 mmHg, Case 2: 111–144/64–79 mmHg). As well, they developed no sudden increase of intracranial pressure such as meningitis, acute hydrocephalus, venous sinus thrombosis, or physiologic events including strong sneezing or coughing.

Therefore, it is important to determine when to discontinue and restart DOACs to avoid bleeding in invasive neurosurgical procedures. According to the previous reports,^[3,7,10] surgical risk and kidney function (creatinine clearance) should be taken into account when deciding when to discontinue DOACs. For the anticipated bleeding risk of neurosurgical surgeries as craniotomy including cerebral aneurysm clipping, spinal surgeries, endovascular surgeries, deep brain or spinal cord stimulation, ventriculoperitoneal shunt, and pituitary surgery is not low (2-day risk of bleed < 2%), but intermediate/high (2-day

risk of bleed, $\geq 2\%$).^[19] Therefore, the present two cases had high bleeding risks. In Case 1, since the creatinine clearance was 85.2 ml/min/1.73 m², it was correct that apixaban was discontinued at 72 h. In Case 2, dabigatran was discontinued at 48 h, but the creatinine clearance was 58.2 ml/min/1.73 m²; dabigatran should be discontinued 72 h or more before surgery. On the other hand, the timing of the postoperative restart of DOACs did not significantly affect the occurrence of bleeding complications,^[6] and thromboembolic events after DOAC discontinuation occurred in 1–2% of patients in previous cohorts.^[5,9] The risk of thromboembolic events when discontinuing DOACs for a longer period in neurosurgical patients remains ambiguous, and further studies are warranted. Both of the present patients restarted DOACs 29 h after surgery. However, from a literature review,^[18] the critical time period during which a significant hematoma may develop has been within 24–48 h after craniotomy. Therefore, in the present two patients who had a low stroke risk based on the CHADS₂-VASc score, the time to the restart of DOAC might be recommended to be at least 48 h or more after surgery. In addition, the heparin-

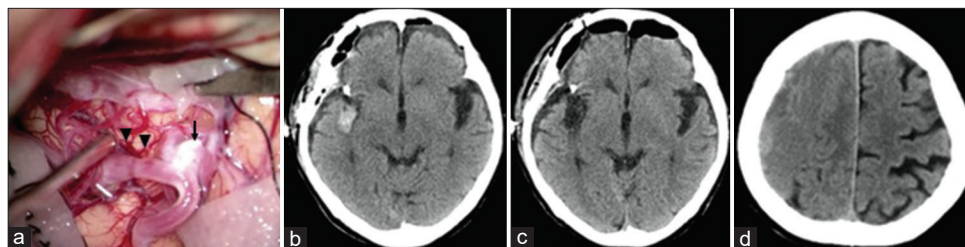


Figure 3: Case 2 (a) During surgical clipping for an aneurysm (arrow) of the right middle cerebral artery, a thin and pial artery bleeds slightly at 2 points of the right temporal lobe (arrowheads), and hemostasis is easily achieved using cotton. (b) Computed tomography (CT) 19 h after surgery shows no evidence of intracranial hemorrhage. (c) CT 94 h after restarting dabigatran shows subarachnoid hemorrhage in the right Sylvian fissure. (d) CT 864 h after surgery shows a right chronic subdural hematoma.

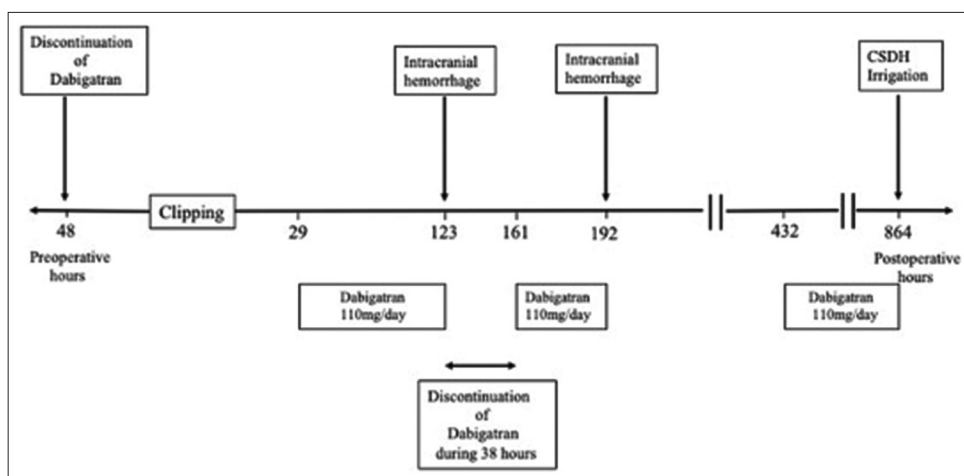


Figure 4: The clinical time course of Case 2.

Table 1: Recommended durations for discontinuation of DOACs based on neurosurgical bleeding risk and creatinine clearance as an indicator of patient renal function.^[3,7,10]

Creatinine clearance (mL/min)	Rivaroxaban, apixaban, and edoxaban (h)	Dabigatran (h)
≥80	≥48	≥48
50–80	≥48	≥72
30–49	≥48	≥96
15–29	≥72	≥120
<15	Not indicated	Not indicated

For the anticipated bleeding risk of neurosurgical surgeries, as craniotomy including cerebral aneurysm clipping, craniectomy, all spinal surgeries, cerebral angiogram, carotid stenting, intracranial or spinal embolization, stroke embolectomy, peripheral decompression, deep brain or spinal cord stimulation, ventriculoperitoneal shunt, lumbar puncture, and pituitary surgery are not low (2-day risk of bleed <2%), but intermediate/high (2-day risk of bleed, ≥2%)^[19]

DOAC bridge in Case 1 should not be necessary in DOAC-treated patients before and after surgery, because it leads to a significantly higher periprocedural bleeding rate without a lower thromboembolism rate, as with heparin-Vitamin K antagonists.^[5,8] From another perspective, both Cases 1 and

2 had type O blood. Factor VIII activity has been reported to be 20–30% lower in subjects with type O blood than in those with other blood types.^[17,21] Patients with type O blood were reported to have^[13] or not have^[16] the potential for postoperative bleeding; however, one should be careful with these patients on DOACs requiring invasive cranial surgery, including cerebral aneurysm clipping. In summary, discontinuation of DOACs should be individualized based on neurosurgical bleeding risk and patient renal function [Table 1].^[4,9,12] Overall, there is a lack of studies for when and at what dose to restart the DOACs after neurosurgical procedures, but restarting DOACs for these patients could be considered to wait at least 48 h, when hemostasis has been achieved.^[5] Bridging of the DOACs cannot be recommended.

CONCLUSION

Two cases of patients who developed intracranial hemorrhage associated with DOAC use after surgical clipping for unruptured cerebral aneurysms were presented. These cases will help neurosurgeons assess risks in patients on DOACs requiring craniotomy.

Acknowledgments

This work was partly supported by a Grant-in-Aid for Strategic Medical Science Research (S1491001) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, a Research Grant of Japanese National Hospital Organization Kamaishi Hospital and a grant from JSPS KAKENHI (21K09158).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Koji T, Kubo Y, Matsumoto Y, Akamatsu Y, Chida K, Kashimura H, *et al.* Intracranial hemorrhage associated with direct oral anticoagulant after clipping for an unruptured cerebral aneurysm: A report of two cases. *Surg Neurol Int* 2022;13:104.