ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.surgicalneurologyint.com

Surgical Neurology International

Editor-in-Chief: Nancy E. Epstein, MD, Clinical Professor of Neurological Surgery, School of Medicine, State U. of NY at Stony Brook.

SNI: Trauma

Editor
Jutty Parthiban, MCh., FNS
Kovai Medical Center and Hospital, Tamil Nadu, India

SNI
Open Access

Case Report

Cerebral infarction following administration of andexanet alfa for anticoagulant reversal in a patient with traumatic acute subdural hematoma

Arata Nagai[1], Hiroshi Karibe[1], Ayumi Narisawa[1], Motonobu Kameyama[1], Shuichi Ishikawa[2], Naoya Iwabuchi[2], Teiji Tominaga[3]

[1]Department of Neurosurgery, Sendai City Hospital, Sendai, Miyagi, [2]Department of Neurosurgery, Isinomaki Red Cross Hospital, Ishinomaki, [3]Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan.

E-mail: *Arata Nagai - longnew0629@gmail.com; Hiroshi Karibe - karibe319759@gmail.com; Ayumi Narisawa - ayunarisawa@gmail.com; Motonobu Kameyama - motokame@qk9.so-net.ne.jp; Shuichi Ishikawa - siskw3911@gmail.com; Naoya Iwabuchi - d06sm013@yahoo.co.jp; Teiji Tominaga - tomi@nsg.med.tohoku.ac.jp

***Corresponding author:**
Arata Nagai,
Department of Neurosurgery,
Sendai City Hospital, Sendai,
Miyagi, Japan.

longnew0629@gmail.com

Received : 23 April 2023
Accepted : 25 July 2023
Published : 11 August 2023

DOI
10.25259/SNI_358_2023

Quick Response Code:

ABSTRACT

Background: Anticoagulants prevent thrombosis in patients with atrial fibrillation (AF) and venous thromboembolism but increase the risk of hemorrhagic complications. If severe bleeding occurs with anticoagulant use, discontinuation and rapid reversal are essential. However, the optimal timing for resuming anticoagulants after using reversal agents remains unclear. Here, we report early cerebral infarction following the use of andexanet alfa (AA), a specific reversal agent for factor Xa inhibitors, in a patient with traumatic acute subdural hematoma (ASDH). The possible causes of thromboembolic complication and the optimal timing for anticoagulant resumption are discussed.

Case Description: An 84-year-old woman receiving rivaroxaban for AF presented with impaired consciousness after a head injury. Computed tomography (CT) revealed right ASDH. The patient was administered AA and underwent craniotomy. Although the hematoma was entirely removed, she developed multiple cerebral infarctions 10 h after the surgery. These infarctions were considered cardiogenic cerebral embolisms and rivaroxaban was therefore resumed on the same day. This case indicates the possibility of early cerebral infarction after using a specific reversal agent for factor Xa inhibitors.

Conclusion: Most studies suggest that the safest time for resuming anticoagulants after using reversal agents is between 7 and 12 days. The present case showed that embolic complications may develop much earlier than expected. Early readministration of anticoagulant may allow for adequate prevention of the acute thrombotic syndromes.

Keywords: Acute subdural hematoma, Andexanet alfa, Anticoagulant, Cerebral infarction

INTRODUCTION

Direct oral anticoagulants (DOAC), including factor Xa inhibitors, reduce the incidence of thromboembolic events in patients with atrial fibrillation (AF) or venous thromboembolism.[25,30,32,34,45] Intracranial hemorrhage (ICH) is one of the most significant complications of DOAC.[3] DOAC-induced coagulopathy often enlarges ICH, resulting in poor outcome.[21] Adequate supportive care and discontinuation of DOAC are essential for bleeding

management. In addition, rapid reversal of anticoagulation provides hemostasis, which improves clinical outcomes. Andexanet alfa (AA) is a modified recombinant inactive form of human factor Xa that specifically reduces anti-factor Xa activity.[1,5,6,24,38] When reversal of factor Xa inhibitors is needed due to life-threatening or uncontrolled bleeding, the administration of AA is considered.

While the efficacy of such reversal agents is being established, the timing of anticoagulant therapy resumption remains controversial. After reversal of anticoagulant therapy, the risk of thromboembolic events increases with delays in anticoagulant resumption. Clinicians must make the difficult decision regarding when to resume anticoagulants.

Anticoagulant-associated traumatic acute subdural hematoma (ASDH) is a devastating injury with high morbidity and mortality.[2,3,8,20,35] In the acute phase of traumatic ASDH, coagulation and fibrinolytic activity changes dynamically and may adversely affect complicated injuries. The risk of thrombotic events is high in the 1st week because of a prothrombotic state induced by trauma.[27,31,40] The risk remains high until anticoagulant therapy is resumed. The pathophysiology of traumatic ASDH may not be the same as that of spontaneous ICH in terms of coagulation and fibrinolytic disorders.

In this report, we present a case of traumatic ASDH during anticoagulation therapy that resulted in early cerebral infarction after AA administration. We also discuss the timing of anticoagulant resumption in patients with traumatic ASDH who received anticoagulant reversal agents. The study participant provided informed consent and the study design was approved by the appropriate Ethics Review Board.

CASE REPORT

An 84-year-old woman with a medical history of AF, hypertension, diabetes mellitus, and cerebral infarction and who was receiving rivaroxaban (15 mg/day) experienced frequent falls in her residential facility due to delirium. She then developed a consciousness disorder on awakening. She was transferred to our hospital with a diagnosis of the right ASDH [Figure 1a]. The Glasgow Coma Scale score was 6. Her pupils were equal and round, and reactive to light and movement. Plasma fibrinogen concentration at admission (332 mg/dL) was within the normal range; however, D-dimer concentration was elevated (6.78 μg/mL). The Prothrombin Time-International Normalized Ration (1.16) was not prolonged. AA (400 mg) was intravenously administered 16 h after the last rivaroxaban oral administration, followed by a continuous infusion of 4 mg/min for 120 min. The patient

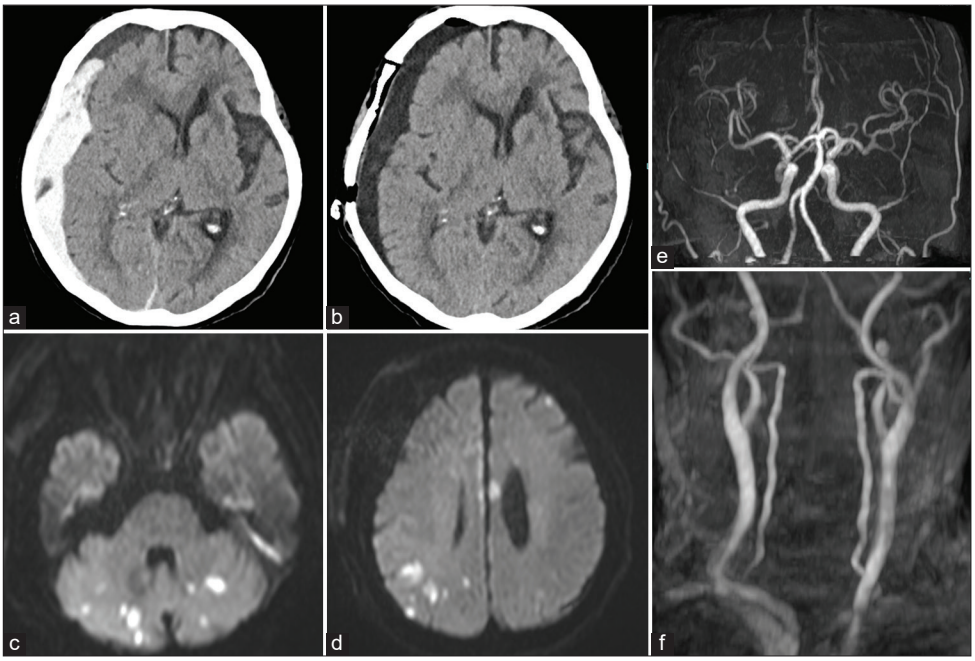

Figure 1: Neuroradiological findings of the case. (a) Plain computed tomography (CT) taken at admission showing a right-sided acute subdural hematoma with low-density areas in some places. (b) CT immediately after surgery showing total subdural hematoma removal and effective intracranial decompression. (c and d) Magnetic resonance imaging taken the day after surgery showing multiple acute cerebral infarctions in the bilateral cerebellar hemispheres, corpus callosum, and cerebral cortex. (e and f) Magnetic resonance angiography showed no vascular abnormalities such as cerebral vascular stenosis, occlusion, or vasospasm.

subsequently underwent surgery. Stable hemostasis was achieved during the surgery, resulting in blood loss of 100 mL. Although AF persisted during surgery, no hypotensive events occurred, and mean blood pressure was always above 65 mmHg. An immediate postoperative computed tomography (CT) scan revealed complete ASDH removal [Figure 1b]; however, the patient had poor postoperative arousal. Brain magnetic resonance imaging showed multiple fresh cerebral infarctions day after the surgery [Figures 1c and d]. Magnetic resonance angiography showed no injury or stenosis of carotid and vertebral arteries [Figures 1e and f]. Postoperative blood tests showed that D-dimer concentration peaked at 4.78 μg/mL and there was no evidence of disseminated intravascular coagulation. On the day of the onset of cerebral infarction, transthoracic echocardiography was performed, which revealed no intracardiac thrombus and no evidence of the right-to-left shunt. Lower limb venous ultrasound demonstrated no venous thrombus in her both legs. These infarctions were considered cardiogenic cerebral embolisms and rivaroxaban was resumed on the same day. Two months later, she was transferred to a long-term care hospital with a modified Rankin Scale of 5.

DISCUSSION

Anticoagulant therapy is effective in preventing ischemic disease in patients with AF, mechanical cardiac valve replacement, or deep venous thrombosis. In contrast, it increases the risk of poor outcomes in patients with traumatic ASDH, mainly resulting from the size or delayed enlargement of the hematoma.[11,18,23,29,42,46] Pretraumatic conditioning with anticoagulants is closely associated with "talk and deteriorate" in patients with ASDH.[19,44] Thus, anticoagulant reversal should be considered in cases of life-threatening bleeding or when surgery is required. AA, recently approved as a specific reversal agent for factor Xa inhibitors, can effectively normalize coagulopathy in such situations. Stable hemostasis was obtained both intra and postoperatively in the present case.

On the other hand, discontinuation and/or reversal of anticoagulants may increase the risk of thromboembolic complications. In the present case, cardiogenic embolic infarctions occurred within a day after reversal of anticoagulation with AA. The mechanism of thromboembolic complications may be related to the following factors: (1) characteristics of the reversal agent itself, (2) underlying personal health condition, and (3) pathogenesis of the hemorrhage.

Thromboembolic risk related to characteristics of the reversal agent

It is believed that AA does not exert procoagulant effects. It is unable to cleave prothrombin into thrombin because the serine in the active site is replaced by alanine.[1] However, the 30-day thromboembolic rate was 9.7% in the ANNEXA-4 study.[6] A meta-analysis suggested that the incidence of thrombotic complications was 10.7%, which is more frequent than in other DOAC reversal agents.[12] Recently, it has been demonstrated that the independent procoagulant effect of AA is mediated by the inhibition of the tissue factor pathway inhibitor (TFPI).[24] Since TFPI is a major inhibitor of the factor VIIa complex, a decrease in its activity may lead to increased thrombogenesis. AA also affects endogenous modulators that regulate hemostasis, including antithrombin and glycosaminoglycan.[38] It may promote a procoagulant environment by disrupting anticoagulation at multiple sites in addition to reducing anti-factor Xa activity.

Thromboembolic risk related to underlying disease

The risk of thromboembolic complications may be different in each patient depending on the underlying disease for which anticoagulation is introduced. It is suggested that anticoagulants should be resumed earlier than previously thought, approximately 3 days after medical presentation.[17] The case reported here had underlying chronic AF, with a $CHADS_2$ score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke [double weight]) score of 6. Thus, the risk of embolism with the withdrawal of anticoagulants was high.[40]

Thromboembolic risk related to the pathogenesis of the hemorrhage

The patient had sustained traumatic ASDH. The coagulation/fibrinolytic system may be abnormal in traumatic hemorrhage compared with nontraumatic hemorrhage, resulting in postoperative hypercoagulability.[9,16] Trauma-induced release of tissue factors into the systemic circulation instigates the extrinsic pathway. It may invoke diffuse intravascular activation of coagulation, leading to fibrin deposition and thromboembolic ischemia.[9,13,47] The incidence of posttraumatic cerebral infarction (PTCI) is approximately 10%.[43,49] The mechanisms of PTCI include embolism, hypercoagulable state, vascular compression, vasospasm, and blunt cerebrovascular injury.[14,49,50]

PTCI of the occipital lobe is well described and often results from compression of the posterior cerebral artery against the tentorium by the herniating medial temporal lobe. Middle cerebral artery territory infarcts may occur as a result of displacement from mass lesions and herniation as well. Cerebral infarction in this case did not depend on the area of vascular control; the multiple small infarcts suggest a cause other than cerebral herniation. Other mechanisms may include vasospasm or thromboembolic events from injured carotid and vertebral arteries. However, magnetic resonance

angiography demonstrated no concomitant vascular injury in this patient. Based on the above, the discontinuation of anticoagulants and use of the reversal agent were likely involved in the embolism in this case.

Appropriate time to resume anticoagulants

It appears safe to discontinue anticoagulation for brief periods in nontraumatic anticoagulant-related cerebral hemorrhage.[30,34] In principle, anticoagulation should be resumed as soon as the bleeding risk is reduced.[6,12,22,32,37,48] However, there are no consensus guidelines for resuming anticoagulation therapy after traumatic ASDH. Traumatic ASDH is a different entity compared with spontaneous ICH, as injured patients are more hypercoagulable than the general population. Table 1 summarizes previous reports on the initiation of anticoagulants after traumatic brain injury (TBI). All reports concluded that anticoagulation resumption decreased the incidence of ischemic stroke and all-cause mortality, whereas the incidence of hemorrhagic complications remained the same or increased. The resumption time was approximately 7–12 days after the injury.

Three of the reports summarized in Table 1 used a specific reversal agent for anticoagulants in the acute phase. According to a report from a Level I trauma center in the United States, 7–9.5 days after injury was the appropriate resumption time,[36] whereas the Japan Head Trauma Data Bank reported the median time for resuming anticoagulants as 9 days after injury.[41] Furthermore, Haji *et al*. reported anticoagulant resumption in 2–16 days in patients with TBI aged >65 years.[15] In particular, patients with mechanical valves and those at high risk of embolism should resume anticoagulants as early as possible, that is within 2–3 days after injury.

There have been some reports of heparin initiation in the hyperacute phase within 24 h after injury for deep vein thrombosis prevention.[4,7,26,33] Shahan *et al*. reviewed 93 patients with blunt cerebrovascular injury who were immediately infused with low-dose heparin during hospitalization.[39] There was no increase in the likelihood of worsening hemorrhage compared to patients without heparin administration. Thus, it may be acceptable to start anticoagulants in the hyperacute phase in patients with traumatic ASDH, if hemostasis has been restored. A multicenter randomized trial (Restart Traumatic Intracranial Hemorrhage) is currently underway to determine when to restart DOAC in patients with TBI, and the results are awaited.[28]

As observed in the present case, cerebral infarction sometimes occurs early after reversal agent use. A meta-analysis of taking anticoagulants showed all thromboembolic complication occurred within a few days (1–4 days) of reversal agent administration.[10] Therefore, early resumption of anticoagulants should be considered for embolism prevention. In fact, no thromboembolic events were observed after resumption of oral anticoagulation in the ANNEXA-4 study.[6] As AA has only been approved for a short time, analysis of real-world data on embolic complications after use in patients with traumatic ASDH is warranted. At present, the resumption of anticoagulants must be determined after considering the risk of bleeding and thromboembolic complications in each patient. It is desirable to establish the criteria for anticoagulant resumption in patients with traumatic ASDH through accumulation of cases.

CONCLUSION

AA was used as an effective reversal agent to achieve hemostasis in a patient with traumatic ASDH. The patient had thromboembolic events, and it cannot be ruled out that

Table 1: Summary of reports on resuming anticoagulant after traumatic brain injury.

Authors	Indications for AC	Type of AC	Number of patients	Use of the reversal agent	Days to resuming AC		Hemorrhagic complication after resuming AC (%)
					Mean	Range	
Wijdicks *et al.* (1998)	MV	VKA	20	FFP	8	2 - 90	0
Byrnes *et al.* (2012)	VTE	UFH	26	N/A	12	0 - 24	3.8
Shahan *et al.* (2014)	BCVI	UFH	93	N/A	0	N/A	9
Matsushima *et al.* (2016)	MV,NVAF, VTE	UFH, VKA	72	N/A	9	4 - 17	8.3
Pandya *et al.* (2018)	VTE	UFH, VKA	35	N/A	8.8	0 - 17	9.1
Puckett *et al.* (2018)	NVAF	VKA	53	FFP, PCC	7	1 - 31	1.8
Divito *et al.* (2019)	VTE	UFH, VKA	105	N/A	8	1 - 31	3
Suehiro *et al.* (2019)	N/A	DOAC, VKA	66	FFP, PCC	9	2 - 66	N/A
Haji *et al.* (2020)	MV, NVAF	DOAC, VKA	15	IDARU, PCC	N/A	2 - 16	0
Matsuhima *et al.* (2021)	NVAF, VTE	DOAC, VKA	168	N/A	10	5 - 17	9.6

AC: Anticoagulant; BCVI: Blunt cerebrovascular injury; DOAC: Direct oral anticoagulant medications; FFP: Fresh frozen plasma; IDARU: Idarucizumab; MV: Mechanical valve; N/A: Not available; NVAF: Non-valvular artiarl fibrillation; PCC: Prothrombin complex concentrate; UFH: Unfractionated heparin; VKA: Vitamin K antagonists; VTE: Venous thromboembolism

AA may have been a contributing factor to their occurrence. In patients with traumatic ASDH treated with AA, early anticoagulant resumption may need to be considered because of the higher embolization risk. More real-world studies on AA use, including the timing of anticoagulant resumption, will greatly add to our knowledge and comfort in using this important drug.

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.

REFERENCES

1. Abuan I, Wong KH, Bolinske B, Hale KS. Andexanet alfa: A recombinant modified human factor Xa protein for drug reversal of rivaroxaban and apixaban. J Pharm Technol 2019;35:119-25.
2. Batchelor JS, Grayson A. A meta-analysis to determine the effect of anticoagulation on mortality in patients with blunt head trauma. Br J Neurosurg 2012;26:525-30.
3. Becattini C, Franco L, Beyer-Westendorf J, Masotti L, Nitti C, Vanni S, *et al*. Major bleeding with vitamin K antagonists or direct oral anticoagulants in real-life. Int J Cardiol 2017;227:261-6.
4. Byrnes MC, Irwin E, Roach R, James M, Horst PK, Reicks P. Therapeutic anticoagulation can be safely accomplished in selected patients with traumatic intracranial hemorrhage. World J Emerg Surg 2012;7:25.
5. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, *et al*. Full study reort of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med 2019;380:1326-35.
6. Demchuk AM, Yue P, Zotova E, Nakamya J, Xu L, Milling TJ, *et al*. Hemostatic efficacy and anti-FXa (factor Xa) reversal with andexanet alfa in intracranial hemorrhage: ANNEXA-4 substudy. Stroke 2021;52:2096-105.
7. Divito A, Kerr K, Wilkerson C, Shepard S, Choi A, Kitagawa RS. Use of anticoagulation agents after traumatic intracranial hemorrhage. World Neurosurg 2019;123:25-30.
8. Dossett LA, Riesel JN, Griffin MR, Cotton BA. Prevalence and implications of preinjury warfarin use: An analysis of the National Trauma Databank. Arch Surg 2011;146:565-70.
9. Epstein DS, Mitra B, O'Reilly G, Rosenfeld JV, Cameron PA. Acute traumatic coagulopathy in the setting of isolated traumatic brain injury: A systematic review and meta-analysis. Injury 2014;45:819-24.
10. Francesco D, Chiara M, Matteo GP, Mark C, David G, Elaine H, *et al*. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of viamin K antagonists. Thromb Haemost 2011;106:429-38.
11. Franko J, Kish KJ, O'Connell BG, Subramanian S, Yuschak JV. Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma. J Trauma 2006;61:107-10.
12. Gómez-Outes A, Alcubilla P, Calvo-Rojas G, Terleira-Fernández AI, Suárez-Gea ML, Lecumberri R, *et al*. Meta-analysis of reversal agents for severe bleeding associated with direct oral anticoagulants. J Am Coll Cardiol 2021;77:2987-3001.
13. Goodnignt SH, Kenoyer G, Rapaport SI, Patch MJ, Lee JA, Kurze T. Defibrination after brain-tissue destrution: A serious complication of head injury. N Engl J Med 1974;290:1043-7.
14. Grigorian A, Kabutey NK, Schubl S, de Virgilio C, Joe V, Dolich M, *et al*. Blunt cerebrovascular injury incidence, stroke-rate, and mortality with the expanded Denver criteria. Surgery (United States) 2018;164:494-9.
15. Haji K, Suehiro E, Kiyohira M, Hujiyama Y, Suzuki M. Effect of antithrombotic drugs reversal on geriatric traumatic brain injury Japan. No Shinkei Geka 2020;48:497-504.
16. Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI. Coagulation disorders after traumatic brain injury. Acta Neurochir (Wien) 2008;150:165-75.
17. Hawryluk GW, Austin JW, Furlan JC, Lee JB, O'Kelly C, Fehlings MG. Management of anticoagulation following central nervous system hemorrhage in patients with high thromboembolic risk. J Thromb Haemost 2010;8:1500-8.
18. Inamasu J, Nakatsukasa M, Kuramae T, Nakagawa Y, Miyatake S, Tomiyasu K. Influence of age and anti-platelet/anti-coagulant use on the outcome of elderly patients with fall-related traumatic intracranial hemorrhage. Neurol Med Chir (Tokyo) 2010;50:1051-5.
19. Itshayek E, Rosenthal G, Fraifeld S, Perez-Sanchez X, Cohen JE, Spektor S. Delayed posttraumatic acute subdural hematoma in elderly patients on anticoagulation. Neurosurgery 2006;58:851-6.
20. Karibe H, Hayashi T, Narisawa A, Kameyama M, Nakagawa A, Tominaga T. Clinical characteristics and outcome in elderly patients with traumatic brain injury: For establishment of management strategy. Neurol Med Chir (Tokyo) 2017;57:418-25.
21. Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, *et al*. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA 2015;313:824-36.
22. Kuramatsu JB, Sembill JA, Gerner ST, Sprügel MI, Hagen M, Roeder SS, *et al*. Management of therapeutic anticoagulation in patients with intracerebral haemorrhage and mechanical heart valves. Eur Heart J 2018;39:1709-23.
23. Lavoie A, Ratte S, Clas D, Demers J, Moore L, Martin M, *et al*. Preinjury warfarin use among elderly patients with closed head injuries in a trauma center. J Trauma 2004;56:802-7.
24. Lu G, Hollenbach SJ, Baker DC, Tan S, Hutchaleelaha A, Curnutte JT, *et al*. Preclinical safety and efficacy of andexanet alfa in animal models. J Thromb Haemost 2017;15:1747-56.
25. Maeda K, Koga M, Okada Y, Kimura K, Yamagami H, Okuda S, *et al*. Nationwide survey of neuro-specialists' opinions on anticoagulant therapy after intracerebral hemorrhage in patients with atrial fibrillation. J Neurol Sci 2012;312:82-5.
26. Matsushima K, Inaba K, Cho J, Mohammed H, Herr K,

Leichtle S, *et al*. Therapeutic anticoagulation in patients with traumatic brain injury. J Surg Res 2016;205:186-91.
27. Milling TJ, Refaai MA, Goldstein JN, Schneider A, Omert L, Amy H, *et al*. Thromboembolic events after vitamin K antagonist reversal with 4-factor prothrombin complex concentrate: Exploratory analyses of two randomized, plasma-controlled studies. Ann Emerg Med 2016;67:96-105.
28. Milling TJ Jr., Warach S, Johnston SC, Gajewski B, Costantini T, Price M, *et al*. Restart TICrH: An adaptive randomized trial of time intervals to restart direct oral anticoagulants after traumatic intracranial hemorrhage. J Neurotrauma 2021;38:1791-8.
29. Mina AA, Knipfer JF, Park DY, Bair HA, Howells GA, Bendick PJ. Intracranial complications of preinjury anticoagulation in trauma patients with head injury. J Trauma 2002;53:668-72.
30. Murthy SB, Gupta A, Merkler AE, Navi BB, Mandava P, Iadecola C, *et al*. Restarting anticoagulant therapy after intracranial hemorrhage: A systematic review and meta-analysis. Stroke 2017;48:1594-600.
31. Nielsen PB, Larsen TB, Skjøth F, Lip GY. Outcomes associated with resuming warfarin treatment after hemorrhagic stroke or traumatic intracranial hemorrhage in patients with atrial fibrillation. JAMA Intern Med 2017;177:563-70.
32. Osaki M, Koga M, Maeda K, Hasegawa Y, Nakagawara J, Furui E, *et al*. A multicenter, prospective, observational study of warfarin-associated intracerebral hemorrhage: The SAMURAI-WAICH study. J Neurol Sci 2015;359:72-7.
33. Pandya U, Pattison J, Karas C, O'Mara M. Does the presence of subdural hemorrhage increase the risk of intracranial hemorrhage expansion after the initiation of antithrombotic medication? Am Surg 2018;84:416-21.
34. Pennlert J, Overholser R, Asplund K, Carlberg B, Van Rompaye B, Wiklund PG, *et al*. Optimal timing of anticoagulant treatment after intracerebral hemorrhage in patients with atrial fibrillation. Stroke 2017;48:314-20.
35. Prexl O, Bruckbauer M, Voelckel W, Grottke O, Ponschab M, Maegele M, *et al*. The impact of direct oral anticoagulants in traumatic brain injury patients greater than 60-years-old. Scand J Trauma Resusc Emerg Med 2018;26:20.
36. Puckett Y, Zhang K, Blasingame J, Lorenzana J, Parameswaran S, Brooks, MD, *et al*. Safest time to resume oral anticoagulation in patients with traumatic brain injury. Cureus 2018;10:e2920.
37. Sakamoto Y, Nito C, Nishiyama Y, Suda S, Matsumoto N, Aoki J, *et al*. Safety of anticoagulant therapy including direct oral anticoagulants in patients with acute spontaneous intracerebral hemorrhage. Circ J 2019;83:441-6.
38. Sartori M, Cosmi B. Andexanet alfa to reverse the anticoagulant activity of factor XA inhibitors: A review of design, development and potential place in therapy. J Thromb Thrombolysis 2018;45:345-52.
39. Shahan CP, Magnotti LJ, McBeth PB, Weinberg JA, Croce MA, Fabian TC. Early antithrombotic therapy is safe and effective in patients with blunt cerebrovascular injury and solid organ injury or traumatic brain injury. J Trauma Acute Care Surg 2016;81:173-7.
40. Staerk L, Fosbøl EL, Lamberts M, Bonde AN, Gadsbøll K, Sindet-Pedersen C, *et al*. Resumption of oral anticoagulation following traumatic injury and risk of stroke and bleeding in patients with atrial fibrillation: A nationwide cohort study. Eur Heart J 2018;39:1698-705.
41. Suehiro E, Fujiyama Y, Kiyohira M, Haji K, Ishihara H, Nomura S, *et al*. Risk of deterioration of geriatric traumatic brain injury in patients treated with antithrombotic drugs. World Neurosurg 2019;127:e1221-7.
42. Suehiro E, Ishihara H, Fujiyama Y, Kiyohira M, Haji K, Nomura S, *et al*. Corresponding to geriatric traumatic brain injury in patients taking antithrombotic agent. Jpn J Neurosurg 2019;28:614-20.
43. Tawil I, Stein DM, Mirvis SE, Scalea TM. Posttraumatic cerebral infarction: Incidence, outcome, and risk factors. J Trauma 2008;64:849-53.
44. Tierney KJ, Nayak NV, Prestigiacomo CJ, Sifri ZC. Neurosurgical intervention in patients with mild traumatic brain injury and its effect on neurological outcomes. J Neurosurg 2016;124:538-45.
45. Toyoda K, Yasaka M, Iwade K, Nagata K, Koretsune Y, Sakamoto T, *et al*. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: A prospective, multicenter, observational study. Stroke 2008;39:1740-5.
46. Van Den Brand CL, Tolido T, Rambach AH, Hunink MG, Patka P, Jellema K. Systematic review and meta-analysis: Is pre-injury antiplatelet therapy associated with traumatic intracranial hemorrhage? J Neurotrauma 2017;34:1-7.
47. Wafaisade A, Lefering R, Tjardes T, Wutzler S, Simanski C, Paffrath T, *et al*. Acute coagulopathy in isolated blunt traumatic brain injury. Neurocrit Care 2010;12:211-9.
48. Wijdicks EF, Schievink WI, Brown RD, Mullany CJ. The dilemma of discontinuation of anticoagulation therapy for patients with intracranial hemorrhage and mechanical heart valves. Neurosurgery 1998;42:769-73.
49. Wu YG, Chao Y, Gao G, Bao D, Dong Y, Wei X, *et al*. Risk factors for cerebral infarction after moderate or severe traumatic brain injury. Ther Clin Risk Manag 2021;17:433-40.
50. Zhang J, Zhang F, Dong JF. Coagulopathy induced by traumatic brain injury: Systemic manifestation of a localized injury. Blood 2018;131:2001-6.

How to cite this article: Nagai A, Karibe H, Narisawa A, Kameyama M, Ishikawa S, Iwabuchi N, *et al*. Cerebral infarction following administration of andexanet alfa for anticoagulant reversal in a patient with traumatic acute subdural hematoma. Surg Neurol Int 2023;14:286.