



Case Report

# Spontaneous epidural hematoma induced by rivaroxaban: A case report and review of the literature

Andre Marolop Pangihutan Siahaan<sup>1</sup> , Steven Tandean<sup>1</sup> , Bahagia Willibrordus Maria Nainggolan<sup>2</sup> 

<sup>1</sup>Department of Neurosurgery, <sup>2</sup>Undergraduate Program in Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.

E-mail: \*Andre Marolop Pangihutan Siahaan - andremarolop@usu.ac.id; Steven Tandean - steven.tandean@usu.ac.id; Bahagia Willibrordus Maria Nainggolan - bahagianainggolan@gmail.com



**\*Corresponding author:**

Andre Marolop Pangihutan Siahaan,  
Department of Neurosurgery,  
Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.  
andremarolop@usu.ac.id

Received : 07 July 2022  
Accepted : 03 September 2022  
Published : 16 September 2022

DOI  
10.25259/SNI\_608\_2022

Quick Response Code:



## ABSTRACT

**Background:** Trauma is the most frequent reason for epidural bleeding. However, numerous investigation had discovered that anticoagulants such as rivaroxaban could cause epidural hematoma. Here, we present a case of epidural hematoma in young man who got rivaroxaban as treatment of deep vein thrombosis.

**Case Description:** A 27-year-old male with a history of deep vein thrombosis and one month of rivaroxaban medication presented with seizure and loss of consciousness following a severe headache. A CT scan of the head revealed epidural bleeding, and emergency blood clot removal was performed. As a reversal, prothrombin complex was utilized.

**Conclusion:** Rivaroxaban has the potential to cause an epidural hemorrhage. Reversal anticoagulant should be administered before doing emergency surgery.

**Keywords:** Case report, Epidural hematoma, Prothrombin complex concentrate, Rivaroxaban, Spontaneous epidural hematoma

## BACKGROUND

Rivaroxaban is a factor Xa inhibitor that may have a more steady and predictable anticoagulant effect than warfarin.<sup>[26]</sup> In situations of deep vein thrombosis (DVT), this medication, which has a low risk of bleeding, has gained popularity.<sup>[14]</sup> Vascular thrombosis induces platelet aggregation and the coagulation cascade. This fact justifies the addition of antiplatelet therapy to anticoagulant therapy in the treatment of DVT.<sup>[25]</sup> Although rivaroxaban appears to be a superior medicine, clinicians must be familiar with its clinical profile, reversal drugs, and management methods in the event of significant bleeding.<sup>[4]</sup> We present a case of spontaneous epidural hematoma under therapy with rivaroxaban. To the best of our knowledge, this is the first report of rivaroxaban-associated spontaneous epidural hematoma in young age.

## CASE PRESENTATION

A 27-year-old man presented with a sudden onset seizure and a loss of consciousness following a severe headache. The neurological examination revealed a GCS of 9/15 with unequal pupils

(L>R) and left hemiparesis. He was prescribed rivaroxaban 15 mg twice daily for 1 month after being diagnosed with DVT. There was no history of trauma, abnormalities of vascular, bleeding disorder, infection, or cancer, according to the patient's medical history.

The laboratory detected a rise in D-dimer (1500, compared to 500 as a standard). The prothrombin time, INR, activated partial thromboplastin time, and thrombin time were all within the normal range. On head CT, a biconvex, hyperdense lesion consistent with epidural hemorrhage was observed on the left frontal and parietal, with a volume of 50 cc and midline shift [Figure 1].

To remove the epidural hematoma, an emergency craniotomy was performed. There was no evidence of a fractured skull, but the duramater revealed extensive and diffuse bleeding. There was no indication of infection, vascular abnormality, or cancer. Closure was accomplished following dura tenting and meticulous blood control. For reversal, 50 units/kg of prothrombin complex concentrate (PCC) were administered in three doses as a reversal agent. First dose was administered during surgery, second dose was administered after surgery, and third dose was administered 24 h after surgery.

On the following day, the patient regained consciousness. At 1-year follow-up, the patient was doing well and has no neurologic deficit.

## DISCUSSION

The most common cause of epidural hematoma is trauma.<sup>[5]</sup> Approximately 95% of the cases involve skull fractures with subsequent vascular injury.<sup>[27]</sup> A spontaneous epidural hematoma is a rare occurrence. This condition is typically



**Figure 1:** On the left frontoparietal region, a hyperdense biconvex lesion consistent with epidural hemorrhage was observed. The lesion compressed the opposing side, causing a midline shift of greater than 5 mm in width.

accompanied by infection of the paranasal sinuses and middle ear, coagulation disorder, vascular malformation, or cancer.<sup>[15]</sup>

Anticoagulant treatment is standard for DVT. Heparin is the preferred drug, but it requires frequent monitoring and has multiple drug and food interactions.<sup>[32]</sup> New anticoagulants with predictable pharmacokinetics are being developed to eliminate the need for frequent monitoring.<sup>[37]</sup> Rivaroxaban, a direct inhibitor of factor Xa, is a new oral anticoagulant approved by the FDA for the prevention and treatment of DVT. In acute DVT, it is considered a safe and effective alternative anticoagulant.<sup>[7]</sup> Numerous authors have demonstrated that rivaroxaban reduces the risk of intracranial bleeding compared to other antithrombotic medications.<sup>[4,14]</sup>

In the EINSTEIN trial, it was determined that the risk of bleeding was significantly lower with rivaroxaban than with warfarin therapy. Intracerebral bleeding was the leading cause of fatal bleeding, which rivaroxaban appears to reduce.<sup>[2]</sup> Moreover, the ROCKET study revealed that rivaroxaban was associated with a 40% lower risk of intracranial and fatal bleeding than warfarin.<sup>[31]</sup> However, recent reports of intracranial hemorrhage complications among rivaroxaban users started to emerge.<sup>[22]</sup> Beynon *et al.* discovered that the incidence of rebleeding was greater in the rivaroxaban group compared to the antithrombotic group (50% vs. 11%). Low body mass, advanced age, prescribing errors, and the use of multiple anticoagulants are all associated with an increased risk of bleeding.<sup>[36]</sup>

After 1 month of rivaroxaban treatment for DVT, the patient in this case developed epidural hematoma. Numerous studies reported rivaroxaban-related epidural hematoma.<sup>[1,28,29,33]</sup> Age, uncontrolled hypertension, concurrent use of nonsteroidal anti-inflammatory drugs and anti-thrombotics, liver and renal impairment, bleeding disorders, and alcohol consumption increased the risk.<sup>[18]</sup> All patients with spinal subdural hematoma associated with rivaroxaban were older than 53 years old, according to a study.<sup>[29]</sup> Due to an acute increase in venous pressure and bleeding, valveless epidural veins can also rupture and bleed.<sup>[10]</sup> Marchand zone in duramater, which extends anteroposteriorly from the pterional region to within 2–3 cm of the external occipital protuberance, has a larger diameter of the middle meningeal artery and can be easily detached, resulting in epidural hematoma.<sup>[17]</sup>

Commonly epidural hematomas are caused by damage to the middle meningeal artery or its terminal arterial branches (in around 55% of patients), the middle meningeal vein (in 30% of instances), and diploic veins or a ruptured dural venous sinus in the remaining 15%. However, this condition could be worse in the event of a diastatic fracture, in which distinct blood clots are present.<sup>[23]</sup> Rapid decompression of a growing

hemorrhagic mass lesion, such as an epidural hematoma, has been regarded as the standard of care. According to Jeong *et al.*, postponing surgery was strongly associated with a bad outcome.<sup>[12]</sup> There is nevertheless the possibility of inevitable temporal delay, such as the time required to stabilize hemodynamic or correct the coagulation profile.<sup>[21]</sup> We also observed a favorable outcome when blood clot removal was conducted promptly, as in this case.

Few studies have reported the incidence of spontaneous epidural spinal bleeding after rivaroxaban administration. Approximately 10–20 mg of rivaroxaban per day is associated with nontraumatic spinal hematoma incidence.<sup>[38]</sup> The risk of spinal epidural hematoma is also increased when aspirin is taken at the same time.<sup>[35]</sup> However, a study found that even at high doses, rivaroxaban does not directly affect platelet aggregation.<sup>[11]</sup> In a recent study, a 72-year-old woman with paroxysmal atrial fibrillation developed a spontaneous spinal epidural hematoma (SSEH) caused by rivaroxaban. The patient's use of rivaroxaban may be a risk factor for the development of SSEH and a contributor to the patient's poor prognosis.<sup>[28]</sup>

A significant disadvantage of rivaroxaban therapy is the limited knowledge of monitoring methods for bleeding complications. Some of these assessments are quantitative, while others only provide qualitative data. In addition, it is essential to note that the availability of Xa antifactor tests was limited in Indonesia.<sup>[34]</sup> A study found that compared to apixaban, rivaroxaban was associated with a significantly increased risk of major ischemic or hemorrhagic events.<sup>[30]</sup> Another study found that rivaroxaban could significantly reduce the risk of intracranial bleeding in atrial fibrillation patients.<sup>[13]</sup> Regarding rivaroxaban's adverse effects, patients with rivaroxaban-associated side effects may benefit from andexanet alfa.<sup>[8]</sup> Andexanet alpha, also known as factor Xa (recombinant), inactivated-zhzo, was recently authorized for use in the United States and Europe. Andexanet alpha is a recombinant human FXa decoy protein with no catalytic activity. It is a specific reversal agent that binds with high affinity to both direct and indirect FXa inhibitors, such as low-molecular-weight heparin and fondaparinux.<sup>[6]</sup>

A study suggests administering activated charcoal (50 g) to intubated intracranial hemorrhage patients with enteral access and/or those at low risk of aspiration who present within 2 h of oral direct factor Xa inhibitor ingestion.<sup>[9]</sup> If andexanet alfa is unavailable, The Anticoagulant Forum recommends 2000 units of four-factor PCC. PCCs are plasma-derived concentrates of the inactive Vitamin K-dependent clotting factors. Four-factor PCC consists of factors II, VII, IX, and X, whereas three-factor PCC consists primarily of factors II, IX, and X, with negligible or no factor VII concentrations.<sup>[8]</sup> Researchers found that PCC 50 IU/kg administered intravenously significantly restored

PT for 24 h. In a recently reported randomized trial, the efficacy and safety of PCC in comparison to FFP were demonstrated by the faster replenishment of coagulation factors and comparable adverse effects.<sup>[19]</sup> In this case, we used PCC as reversal. PCCs are prepared from plasma from multiple donors that have been inactivated against viruses and contain a variety of coagulation factor combinations and concentrations.<sup>[20]</sup> This case report is expected to provide input for clinicians in the treatment of intracranial hemorrhage in rivaroxaban users.

A study reported anticoagulation reversal strategies should be established without delaying surgical management. In elective surgery, discontinuing rivaroxaban at least 24 h before the procedure is sufficient to normalize the risk of bleeding associated with the drug. In emergency surgery, anti-Factor Xa levels had to be measured. The risk of drug-induced bleeding decreases with each hour between the last rivaroxaban dose and surgery.<sup>[16]</sup> When intracranial hemorrhage is present or suspected, it is necessary to discontinue factor Xa inhibitors.<sup>[9]</sup> The Anticoagulant Forum suggests treating patients treated with a factor Xa inhibitor who require an urgent procedure and who require a reversal agent with andexanet alfa at the same dose used for major bleeding. If andexanet alfa is unavailable, they recommend PCC 2000 units with four factors.<sup>[8]</sup> The next issue is whether or not to resume anticoagulation. In one study, the optimal timing for readministration of Xa anticoagulant was 2–3 weeks postoperatively.<sup>[35]</sup> According to a different study, anticoagulants should be avoided for the first 2 weeks and resuming should be explored after 4 weeks.<sup>[3]</sup> Another study found that resuming anticoagulant therapy between 6 and 8 weeks was associated with a decreased risk of all-cause mortality.<sup>[24]</sup> It would be necessary to conduct additional research to acquire a deeper comprehension of this problem.

## CONCLUSION

Despite the fact that rivaroxaban, a factor Xa inhibitor seems to be a better medication, doctors need to be familiar with its clinical profile, reversal medications, and management strategies in the event of substantial bleeding. Without postponing surgical care, anticoagulation reversal techniques should be developed using andexanet alfa. In contrast, PCC may be used as an anticoagulant reversal if andexanet alfa was not accessible.

## 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

- Bang WS, Kim KT, Park MK, Sung JK, Lee H, Cho DC. Acute spinal subdural hematoma in a patient taking rivaroxaban. *J Korean Med Sci* 2018;33:e40.
- Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, *et al.* Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499-510.
- Becattini C, Sembolini A, Paciaroni M. Resuming anticoagulant therapy after intracerebral bleeding. *Vascu Pharmacol* 2016;84:15-24.
- Chatterjee S, Sardar P, Biondi-Zoccai G, Kumbhani DJ. New Oral anticoagulants and the risk of intracranial hemorrhage: Traditional and bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation. *JAMA Neurol* 2013;70:1486-90.
- Chen H, Guo Y, Chen SW, Wang G, Cao HL, Chen J, *et al.* Progressive epidural hematoma in patients with head trauma: Incidence, outcome, and risk factors. *Emerg Med Int* 2012;2012:134905.
- Crowther M, Cuker A. How can we reverse bleeding in patients on direct oral anticoagulants? *Kardiologia Pol* 2019;77:3-11.
- Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: Focus on new anticoagulant agents. *Blood* 2008;111:4871-9.
- Cuker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, *et al.* Reversal of direct oral anticoagulants: Guidance from the anticoagulation forum. *Am J Hematol* 2019;94:697-709.
- Frontera JA, Lewin JJ 3<sup>rd</sup>, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, *et al.* Guideline for reversal of antithrombotics in intracranial hemorrhage: A statement for healthcare professionals from the neurocritical care society and society of critical care medicine. *Neurocrit Care* 2016;24:6-46.
- Groen RJ, Groenewegen HJ, August H, van Alphen M, Hoogland PV. Morphology of the human internal vertebral venous plexus: A cadaver study after intravenous araldite CY 221 Injection. *Anat Rec* 1997;249:285-94.
- Hernandez-Juarez J, Espejo-Godinez HG, Mancilla-Padilla R, Hernandez-Lopez JR, Moreno JA, Majluf-Cruz K, *et al.* Effects of rivaroxaban on platelet aggregation. *J Cardiovasc Pharmacol* 2020;75:180-4.
- Jeong YH, Oh JW, Cho S, Korean Trauma Data Bank System Committee. Clinical outcome of acute epidural hematoma in Korea: Preliminary report of 285 cases registered in the Korean trauma data bank system. *Korean J Neurotrauma* 2016;12:47-54.
- Jiang H, Jiang Y, Ma H, Zeng H, Lv J. Effects of rivaroxaban and warfarin on the risk of gastrointestinal bleeding and intracranial hemorrhage in patients with atrial fibrillation: Systematic review and meta-analysis. *Clin Cardiol* 2021;44:1208-15.
- Kakkos SK, Kirkkilesis GI, Tsolakis IA. Editor's choice- efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: A systematic review and meta-analysis of phase III trials. *Eur J Vasc Endovasc Surg* 2014;48:565-75.
- Kim BG, Yoon SM, Bae HG, Yun IG. Spontaneous intracranial epidural hematoma originating from dural metastasis of hepatocellular carcinoma. *J Korean Neurosurg Soc* 2010;48:166-9.
- Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther* 2005;78:412-21.
- Lapadula G, Caporlingua F, Paolini S, Missori P, Domenicucci M. Epidural hematoma with detachment of the dural sinuses. *J Neurosci Rural Pract* 2014;5:191-4.
- Liew A, Eikelboom JW, O'Donnell M, Hart RG. Assessment of anticoagulation intensity and management of bleeding with old and new oral anticoagulants. *Can J Cardiol* 2013;29:S34-44.
- Lu G, Deguzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, *et al.* A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat Med* 2013;19:446-51.
- Majeed A, Kim YK, Roberts RS, Holmström M, Schulman S. Optimal timing of resumption of warfarin after intracranial hemorrhage. *Stroke* 2010;41:2860-6.
- Marcoux J, Bracco D, Saluja RS. Temporal delays in trauma craniotomies. *J Neurosurg* 2016;125:642-7.
- Maurice-Szamburski A, Graillon T, Bruder N. Favorable outcome after a subdural hematoma treated with feiba in a 77-year-old patient treated by rivaroxaban. *J Neurosurg Anesthesiol* 2014;26:183.
- Montemurro N, Santoro G, Marani W, Petrella G. Posttraumatic synchronous double acute epidural hematomas: Two craniotomies, single skin incision. *Surg Neurol Int* 2020;11:435.
- Moon JY, Bae GH, Jung J, Shin DH. Restarting anticoagulant therapy after intracranial hemorrhage in patients with atrial fibrillation: A nationwide retrospective cohort study. *Int J Cardiol Hear Vasc* 2022;40:101037.
- Nieswandt B, Pleines I, Bender M. Platelet adhesion and activation mechanisms in arterial thrombosis and ischaemic stroke. *J Thromb Haemost* 2011;9:92-104.
- Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.
- Pujari R, Hutchinson PJ, Kolias AG. Surgical management of traumatic brain injury. *J Neurosurg Sci* 2018;62:584-92.
- Raeouf A, Goyal S, van Horne N, Traylor J. Spontaneous spinal epidural hematoma secondary to rivaroxaban use in a patient with paroxysmal atrial fibrillation. *Cureus* 2020;12:e10417.
- Rahimizadeh A, Malekmohammadi Z, Williamson WL, Rahimizadeh S, Amirzadeh M, Asgari N. Rivaroxaban-induced acute cervical spine epidural hematoma: Report of a case and review. *Surg Neurol Int* 2019;10:210.
- Ray WA, Chung CP, Stein CM, Smalley W, Zimmerman E, Dupont WD, *et al.* Association of rivaroxaban vs apixaban with major ischemic or hemorrhagic events in patients with atrial

- fibrillation. *JAMA* 2021;326:2395-404.
31. ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with Vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: Rationale and design of the ROCKET AF study. *Am Heart J* 2010;159:340-7.e1.
  32. Scaglione F. New oral anticoagulants: Comparative pharmacology with Vitamin K antagonists. *Clin Pharmacokinet* 2013;52:69-82.
  33. Shin S, Kang H, Lee JW, Gyun KH, Choi ES. Epidural hematoma after total knee arthroplasty in a patient receiving rivaroxaban: A case report. *Anesth Pain Med* 2019;14:102-5.
  34. Steiner T, Böhm M, Dichgans M, Diener HC, Ell C, Endres M, *et al.* Recommendations for the emergency management of complications associated with the new direct oral anticoagulants (DOACs), apixaban, dabigatran and rivaroxaban. *Clin Res Cardiol* 2013;102:399-412.
  35. Trujillo T, Dobesh PP. Clinical use of rivaroxaban: Pharmacokinetic and pharmacodynamic rationale for dosing regimens in different indications. *Drugs* 2014;74:1587-603.
  36. Van Dongen CJ, Prandoni P, Frulla M, Marchiori A, Prins MH, Hutten BA. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. *J Thromb Haemost* 2005;3:939-42.
  37. Yeh CH, Hogg K, Weitz JI. Overview of the new oral anticoagulants: Opportunities and challenges. *Arterioscler Thromb Vasc Biol* 2015;35:1056-65.
  38. Zaarour M, Hassan S, Thumallapally N, Dai Q. Rivaroxaban-induced nontraumatic spinal subdural hematoma: An uncommon yet life-threatening complication. *Case Rep Hematol* 2015;2015:275380.

**How to cite this article:** Siahaan AM, Tandean S, Nainggolan BW. Spontaneous epidural hematoma induced by rivaroxaban: A case report and review of the literature. *Surg Neurol Int* 2022;13:420.