

Spontaneous intracranial epidural hematoma during rivaroxaban treatment

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SUMMARY

According to our research, this is the first case described in the literature of spontaneous intracranial epidural hematoma secondary to the use of Xarelto[®]. Spontaneous intracranial epidural hematomas are rarely described in the literature. They are associated with infectious diseases of the skull, coagulation disorders, vascular malformations of the dura mater and metastasis to the skull. Long-term post-marketing monitoring and independent reports will probably detect the full spectrum of hemorrhagic complications of the use of rivaroxaban.

Keywords: cranial epidural hematoma, hemorrhage, cerebrovascular circulation.

Study conducted at Instituto de Neurologia de Curitiba (INC), Curitiba, PR, Brazil

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INTRODUCTION

Epidural hematomas are fairly common in the literature. About 83 to 95% of the cases are associated with skull fractures¹ with vascular injury and detachment of the dura mater from the bone's inner surface.² Except for traumatic causes, this type of hematoma is associated with four etiological categories: pericranial infections (sinusitis, otitis),^{3,4} dural arteriovenous malformations,³ metastases to the bony skull,⁵ and coagulation disorders.⁶

New anticoagulants are emerging, since warfarin requires frequent monitoring, and has multiple drug and food interactions. Rivaroxaban and other new anticoagulants were developed with the goal of predictable pharmacokinetics, which eliminates the need for monitoring the International Normalized Ratio (INR). Previous studies have shown a statistically significant decrease in intracranial hemorrhage with rivaroxaban against warfarin, but the risk still exists.⁷

We describe the first case of spontaneous intracranial epidural hematoma secondary to rivaroxaban use to be published in a medical journal.

CASE REPORT

A 39 year-old male, with a previous hospitalization due to atrial fibrillation with rapid ventricular response and medicated with rivaroxaban (Xarelto[®], Janssen Pharmaceuticals

Inc.). Two months later, he was admitted into our emergency service. The family reported generalized tonic-clonic seizures 2 hours before. This was the first event in his life and there was no reported trauma, not even minor. He temporarily recovered his consciousness but a few minutes later became progressively comatose (lucid interval). On arrival, his Glasgow Coma Score (GCS) was 4, the left pupil was mydriatic and nonreactive, and the Babinski reflex was positive on the right. Emergency orotracheal intubation was performed; blood samples were taken, as well as a brain CT scan, which depicted epidural hematoma on the left with midline deviation (Figure 1 A and B).

Laboratory test results included white blood cells 0.02 x 10⁹/L, hemoglobin 17.29 g/dL, hematocrit 0.50, platelet 401.5 x 10⁹/L, sodium 142 mmol/L, potassium 3.17 mmol/L, creatinine 1.18 µmol/L, urea 2.5 mmol/L, prothrombin time 12.2 seconds, INR 1.07 IU, and partial thromboplastin time (PTT) 23.9 seconds.

A left parietal craniotomy was performed and the epidural hematoma drained. During the surgery, no evidence of trauma was found on the scalp and skull. The hematoma was visualized and drained; coagulation and adherence to the dura mater were found. No signs of infection, arteriovenous fistula or tumor lesions were observed. Coagulation was greatly reduced. Bleeding of the dura mater and bone was diffuse and active, and hemoglobin

level was altered from 17.29 g/dL to 6.0 g/dL. An infusion of 900 mL of concentrated erythrocytes and 1,500 mL of fresh frozen plasma was used. Closure was performed anchoring the dura mater to the bone, and placing an intracranial pressure monitor and a subcutaneous drain. Forwarded to the intensive care unit, the brain CT scan was repeated in the second postoperative period depicting no evidence of hematoma in the surgical field (Figure 1 C and D). Coma lasted for 4 days. He remained hospitalized in rehabilitation and for treatment of respiratory infection being discharged after 40 days, ambulating, speaking with a slight right-sided hemiparesis grade IV.

DISCUSSION

Intracranial epidural hematoma is an uncommon, but serious complication of head injury. While its exact incidence is still unknown, it is estimated at 1 to 4% of traumatic head injury cases, and 5 to 15% of autopsy series. Spontaneous intracranial epidural hematoma is the most uncommon neurological emergency and requires urgent investigation and treatment.⁸

The dura mater is adhered to the bone with its most external layer along the base level and the sutures. There is a region in which the dura can be easily detached from bone surface called the “Marchand Zone”. This zone ex-

tends antero-posteriorly from the pterional region until 2 to 3 cm of the external occipital protuberance. In the cephalocaudal direction, it runs from the middle line to the base of the skull. Whichever the causal mechanism, this region can be easily detached from the skull.⁹

Schneider and Hegarty in 1951 wrote the first report on spontaneous intracranial epidural hematoma. Until this date, only 20 cases were documented in the literature.^{3-6,10} Hematologic abnormalities are associated with up to 8% of all intracerebral hemorrhage cases, including anticoagulant-induced coagulopathy.¹¹ Bleeding events are the most frequent adverse reactions associated with oral anticoagulants. Warfarin anticoagulation increases the risk of intracerebral hemorrhage in two- to five-fold. The risk is directly related to anticoagulation intensity. Nevertheless, most warfarin-associated intracerebral hemorrhage cases occur during times when the drug is in the therapeutic range (INR 2.0-3.0).¹²

The Food and Drug Administration (FDA) approved rivaroxaban (Xarelto®) in 2011, a new orally administered direct factor Xa inhibitor with superior efficacy and a similar safety profile to warfarin, prescribed for stroke, systemic embolism prophylaxis in patients with non valvular atrial fibrillation, treatment, and prevention of pulmonary embolism and deep vein thrombosis. The ROCKET AF

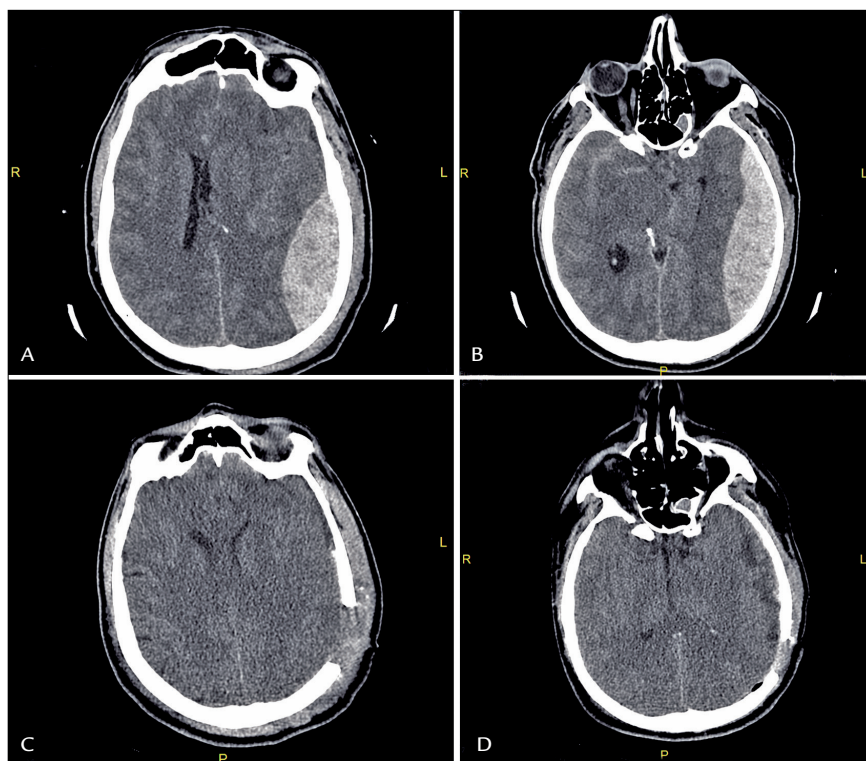


FIGURE 1 A and B. Pre-op CT scan image. C and D. Post-op CT scan image.

study showed that rivaroxaban had 40% lower risk of intracranial and fatal bleeding compared to warfarin.¹³

A recent study about characteristics of intracerebral hemorrhage during rivaroxaban treatment reported its occurrence in patients at high risk for major bleeding. However, when compared with combined warfarin, the hematomas were smaller, had no expansion, and had favorable functional/survival outcomes.¹⁴

In this context, the once-a-day dosage, the need for monitoring the INR, no inferiority to warfarin in treating the atrial fibrillation, and the decreased risk of bleeding in comparison to warfarin have made rivaroxaban an attractive alternative in patients who plan to use this anticoagulant.

Despite the promise to be a medication with better compliance and safer for intracranial hemorrhage, we must be cautious and careful with its use. Traditional coagulation studies do not determine the degree of anticoagulation of rivaroxaban¹⁵ in patients with decreased creatinine clearance as drug exposure is increased, and the risk of bleeding is elevated:¹⁶ both thrombotic and bleeding event rates were higher in patients over the age of 65.¹⁷ It is also contraindicated in patients with hepatic disease associated with coagulopathy,¹⁸ and associated with increased risk of gastrointestinal bleeding compared to warfarin.¹⁹ Moreover, multiple cerebral micro bleeds were detected more frequently in the rivaroxaban group than in the warfarin group.¹⁴

These are important data that we take into account in the selection of the patient for the use of the drug. Even in a young patient, as in the case presented and without other risk factors for bleeding, the use of rivaroxaban can be a triggering factor for the intracranial bleeding. As reported in the described case, the control of bleeding can be extremely difficult. Currently, there are no reports of spontaneous subdural hematomas associated with rivaroxaban. Our patient developed spontaneous subdural hematoma, which is a serious complication, even in the absence of other factors (trauma, renal dysfunction, or uncontrolled blood pressure).

Fresh frozen plasma is unlikely to be effective in patients treated with these drugs who are acutely bleeding. Prothrombin complex concentrate can be considered in patients on rivaroxaban regimen.¹⁵ Assays are needed to establish the degree of anticoagulation produced by rivaroxaban, and to evaluate reversal agents that could be effective in the setting of acute bleeding.

CONCLUSION

Rivaroxaban is a newer anticoagulant that has several advantages compared to traditional anticoagulants. Nevertheless, there are several factors to be considered before prescribing it. To our knowledge, this is the first report

of spontaneous subdural hematoma associated with rivaroxaban usage. Long-term post-marketing monitoring and independent reports will probably detect the full spectrum of hemorrhagic complications triggered by the use of this medication.

RESUMO

Hematoma epidural intracraniano espontâneo durante tratamento com rivaroxaban

Segundo nossa pesquisa, descrevemos o primeiro caso na literatura de hematoma epidural intracraniano espontâneo secundário ao uso de Xarelto®. Hematomas epidurais intracranianos espontâneos raramente são descritos na literatura, sendo comumente associados a doenças infecciosas cranianas, distúrbios de coagulação, malformações vasculares da dura-máter e metástases cranianas. A elaboração de relatórios de monitoramento em longo prazo de pós-comercialização e relatórios independentes provavelmente irá detectar o espectro completo de complicações hemorrágicas do uso desse medicamento.

Palavras-chave: hematoma epidural craniano, hemorragia, circulação cerebrovascular.

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