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CASE REPORT

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Neurosurgery in a patient at peak levels of rivaroxaban: taking into account all factors

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Abstract

We present a patient who underwent urgent neurosurgery for acute onset paraplegia due to a spontaneous subdural spinal hematoma less than 5 hours after she had taken rivaroxaban. The Key Clinical Question was whether early high-risk surgery on a patient taking direct oral anticoagulants is feasible. Prothrombin complex concentrate (PCC) and tranexamic acid were administered and perioperative hemostasis was good. There is scant data on neurosurgical procedures performed within 12 hours after the intake of a direct oral anticoagulant. With the hemostatic support of high-dose PCC, early surgery after administration of rivaroxaban seems feasible in case of an emergency indication, but should only be considered when delaying surgery is esteemed hazardous to the patient. More experience is needed to allow balancing risks and benefits of urgent vs delayed intervention and on the optimal hemostatic support in the absence of a specific antidote.

KEYWORDS

anticoagulants, atrial fibrillation, hemorrhage, hemostasis, spine

Essentials

- There is scant data on surgery shortly after intake of rivaroxaban.
- We performed neurosurgery using high dose PCCs and tranexamic acid.
- Intraoperative haemostasis was good and no transfusion was needed.
- There was no delayed postoperative haemotoma or thromboembolic complication.

1 | INTRODUCTION

Oral anticoagulants are the treatment of choice for prevention of stroke in most patients with nonvalvular atrial fibrillation and for treatment and prevention of venous thromboembolism. Historically, vitamin K antagonists were the only oral anticoagulants for clinical use. Due to the unpredictable pharmacokinetics, regular monitoring of the anticoagulation effect using the international normalized ratio (INR) is required to ensure safe use. Due to its long half-life, the anticoagulant effect persists long after interruption. Although administration of vitamin K reduces the time to INR normalization, this effect requires many hours. Therefore, complexes of clotting factors (prothrombin complex concentrate; PCC) have been used to quickly replenish the coagulation system and urgently restore coagulation in patients treated with vitamin K antagonists.

The work was carried at the University Hospitals Gasthuisberg, Leuven, Belgium.

In the recent decade, other direct oral anticoagulant drugs (DOACs) were developed. Because they can be used without need for monitoring, the tests that measure their anticoagulant effect are less routinely available. Whereas the effect of the thrombin inhibitor dabigatran can be immediately reversed by a specific monoclonal antibody fragment (Idarucizumab),[1] antidotes for the factor Xa inhibitors are still under investigation and are not available for clinical use.[2,3]

Patients taking oral factor Xa inhibitors requiring urgent surgery present a challenge where the urgency of the procedure has to be weighed against the bleeding risk of the residual anticoagulant effect. The Key Clinical Question of this report was whether this high-risk surgery in a patient with very recent DOAC intake was possible, using PCC to support coagulation. The results from in vitro studies, animal studies, and clinical trials have yielded conflicting results.[4] The effect of PCCs on clotting parameters and, where assessed, on blood loss varied with the DOAC studied, the model used, and the dose of PCC. Current guidelines recommend the use of PCCs in a high dose (50 IU/kg) in patients presenting with acute life-threatening bleeding and expected high levels of fXa antagonists, but there is limited guidance for their use in patients requiring reversal who do not present with bleeding. Importantly, PCCs, and especially activated PCCs, have a prothrombotic risk, and the awareness of possible side effects should be taken into account when considering their use.

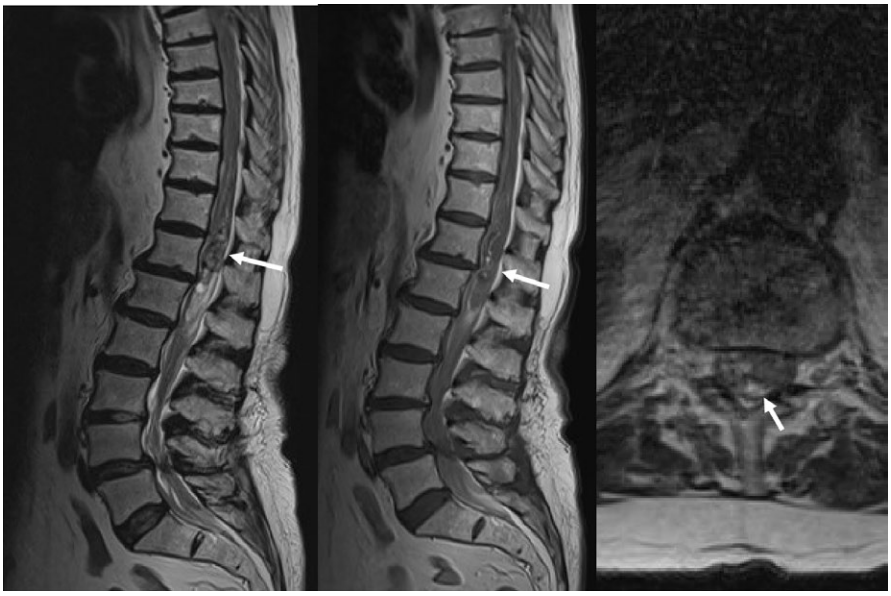

FIGURE 1 Pre-operative MRI: sagittal T2, sagittal T1, axial T2 at the level of T12 hyper intense nodule, suggestive for recent bleeding (white arrows)

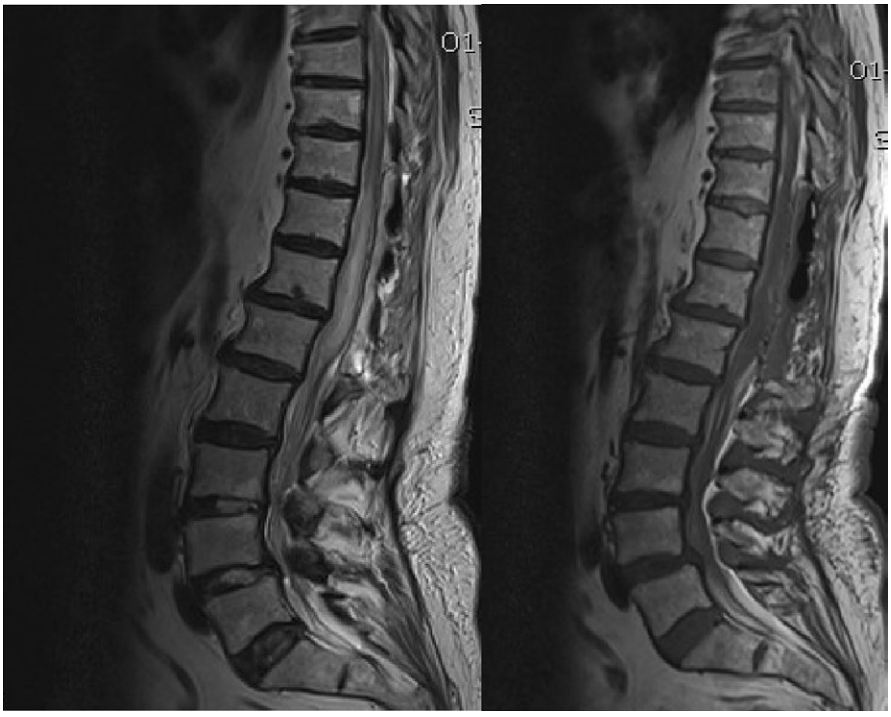

FIGURE 2 Post-operative MRI. Sagittal T2 and sagittal T1, displaying laminectomy T11-L1 and edema in the spinal cord and conus medullaris

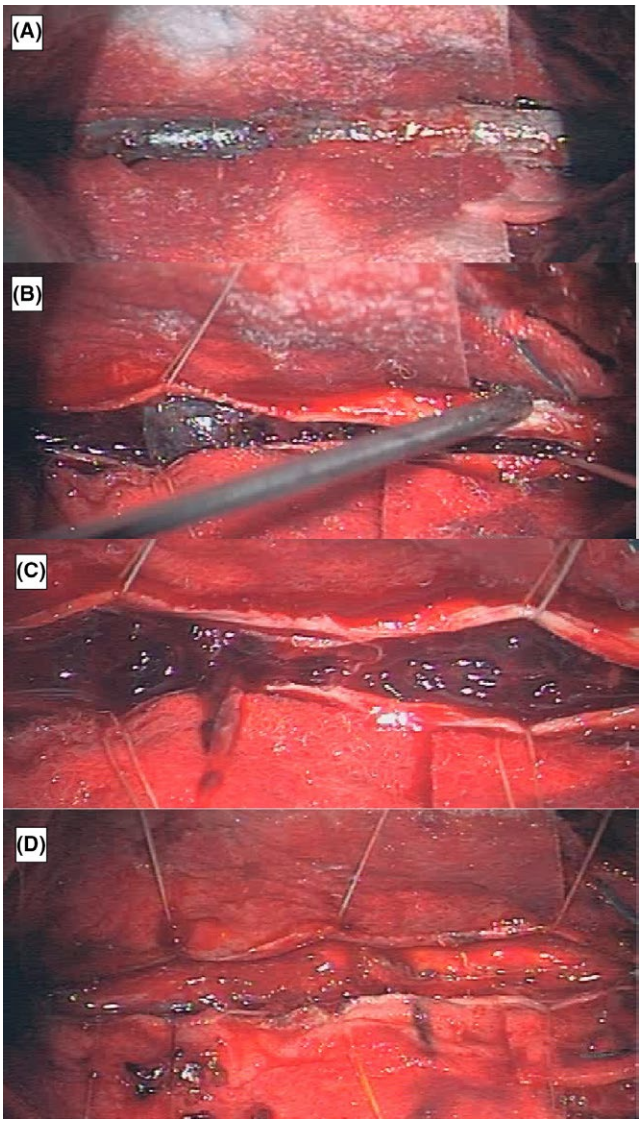

FIGURE 3 Pre-operative images. (A) Bluish-purplish discoloration of the duro. (B) Durotomy, displaying an intradural subacute hemorrhage with webbing. (C) Progressive evacuation of the hematoma. (D) Decompression of the spinal cord and conus medullaris

Spontaneous subdural spinal hematoma is a rare complication in patients on anticoagulant treatment with vitamin K antagonists,[5,6] heparins[7] and DOACs.[8–11]

2 | CASE PRESENTATION

An 80-year old Caucasian female, weighing 72 kg, with an estimated creatinine clearance 60 mL/min/1.73 m^2, presented at our Emergency Department because of excruciating pain in the right leg, arisen abruptly 7 days earlier while vomiting. She had a history of nonvalvular atrial fibrillation, for which she was started on rivaroxaban 15 mg once daily 3 years earlier. At admission, a computed tomography (CT) of the thoracolumbar spine was performed, which was unremarkable. She was hospitalized on the geriatric department for intravenous analgesia. At 8:08 AM on the fourth day of hospitalization, rivaroxaban was administered. During washing afterwards, she remarked not feeling the nurses' touch on her legs and being unable to move her legs. An urgent neurological evaluation showed a flaccid paraplegia with no sensation below T10-T11 level. Magnetic resonance imaging scan revealed a T2 heterogenic mass at the level of T11-L1 (Figure 1).

TABLE 1 Protocol for early surgery in patient treated with rivaroxaban

Immediate administration of 1 g tranexamic acid IV upon decision to operate
Pre-operative administration • 1 g tranexamic acid IV in bolus • PCC 50 U/kg body weight
Peroperative administration • In case of profuse bleeding during operation administration of another 25 U/kg body weight
Post-operative administration • Tranexamic acid IV 1 g 6 times in bolus over 24 hours

IV, intravenously; PCC, prothrombin complex concentrate.

From a neurosurgical point of view, surgery appeared the only treatment with a realistic possibility of neurological recuperation. Because of the lack of available literature and the absence of clear guidance, this case was discussed with the unit of thrombosis and haemostasis of the cardiovascular department. The neurosurgery department decided to operate if the unit of thrombosis and haemostasis could provide a theoretical framework for intraoperative haemostasis normalization. In a pre-operative blood sample, prothrombin time was 25 seconds (normal range 9.4-12.5 seconds; INR 2.1) and activated partial thromboplastin time was 34.9 seconds (normal range 25.1-36.5 seconds); platelet count was 357 10^9/L.

Pre-operatively 50 U/kg of PCC were administered, as well as 2×1 g boluses of tranexamic acid. At 12:40 PM laminectomy and durotomy at the level T11-L1 were performed, demonstrating a subdural hematoma which was evacuated (Figure 2). After closure of the wound, total blood loss was 100 mL. No additional administration of prothrombin complex concentrate (PCC) nor transfusion were necessary. Tranexamic acid (6×1 g in bolus) was continued for 24 hours postoperatively. Rivaroxaban blood levels were 440 ng/mL (chromogenic anti-factor Xa assay, pre-operative sample processed post-operatively), confirming peak levels at the time of surgery (Figure 3).

Immediately post-operatively, the excruciating pain was greatly reduced, but neurological function did not recover. She was transferred for geriatric rehabilitation. Thromboprophylactic enoxaparin was resumed 1 day postoperatively. Rivaroxaban blood levels 17 hours after administration of PCCs was 46 ng/mL, prothrombin time of 14.3 seconds. One month after surgery, there was no neurological recovery, nor any thromboembolic complications.

3 | DISCUSSION

Intracranial and intraspinal hemorrhage is a rare but devastating complication of anticoagulation therapy. Although DOACs significantly

reduce the risk of intracranial bleeding compared with vitamin K antagonists, there is less experience with the management in case of urgent surgery.

While specific tests that allow the assessment of anticoagulant status are available for all NOACs, they are not routinely performed at all laboratories. Given their predictable pharmacokinetics, time since last intake is the most important factor to determine the residual anticoagulant effect. In an emergency situation, identification of the type of anticoagulant, the dose, and the time since last intake are therefore important. As renal insufficiency can prolong the half-life of NOACs, an assessment of renal function is also helpful. Typical routine coagulation assays such as the prothrombin time and activated partial thromboplastin time are influenced by NOACs, but are not linearly correlated with NOAC levels.

In our patient, the prolonged prothrombin time was compatible with the recent intake of rivaroxaban, which was confirmed by the rivaroxaban level using an anti-factor Xa-chromogenic assay. Of note, specific assays may not be available at any hospital and at any time. This case illustrates that the rapid availability of specific coagulation tests can be helpful as a guidance in challenging cases. However, in the absence of such information, time since last dose and renal function can help to approximate the residual anticoagulant activity. In this case, the indication for surgery was present a couple of hours after last intake of rivaroxaban.

In vitro and preclinical studies have shown that the use of prothrombin complex concentrate, which contain coagulation factor II, VII, IX, and X, can counteract the effect of DOACs, especially when administered in a high dose (50 U/kg). PCCs were effective in reducing bleeding in animal models of severe trauma during NOAC treatment.[12] In healthy volunteers who received rivaroxaban or apixaban, PCCs (50 U/kg) reversed the effects on coagulation tests and biopsy-induced bleeding.[13,14] Therefore, PCCs are recommended as a prohemostatic agent in patients treated with a factor Xa inhibitor who present with severe or life-threatening bleeds not responding to conservative measures.[15] For patients treated with the thrombin inhibitor dabigatran, the specific reversal agent idarucizumab can rapidly and completely reverse the anticoagulant effect. Idarucizumab is approved by the Food and Drug Administration and European Medicines Agency in patients with recent intake of dabigatran requiring urgent surgery or presenting with life-threatening bleeding.

This patient, treated with rivaroxaban, presented both with an acute bleeding complication in a critical organ and with the need for an urgent intervention. Diagnosis of the bleeding and indication for surgery was made at the time of expected peak rivaroxaban levels. Administration of PCCs is therefore recommended. In patients without a bleeding but requiring an urgent procedure, an analogous strategy has been proposed (Table 1).

In conclusion, we performed an urgent laminectomy and durotomy with evacuation of the subdural hematoma after administration of PCCs and tranexamic acid less than 5 hours after rivaroxaban intake. Pre- and postoperative hemostasis was assessed as normal. Early surgery after administration of rivaroxaban seems feasible in case of an emergency indication, but more experience is necessary on the hemostatic effects and the thrombotic risk of such strategy. An important inherent limitation of case reports is that we cannot compare outcome of the chosen treatment with alternatives, such as delaying surgery or using other measures of hemostatic support. Therefore, this case by itself cannot compare the relative efficacy or safety of this approach. Nevertheless, the case illustrates that clotting factor concentrates can be considered as an option in patients requiring urgent surgery at peak anticoagulant levels. It also illustrates the importance of interdisciplinary communication in complex patients.

AUTHOR CONTRIBUTIONS

The conception and design of the study was done by P. Verhamme, B. Nuttin and J. De Vlieger, who were on call when this case presented on the ER. The case presentation was drafted by R. Demaerel and S. Dietvorst. The abstract, introduction, and discussion were written by J. De Vlieger and T. Vanassche, as was the revised text. The manuscript was revised and approved by all authors before submission.

RELATIONSHIP DISCLOSURES

Jan De Vlieger, Rik Demaerel, Sofie Dietvorst and Bart Nuttin have no conflicts of interest. Thomas Vanassche has received speaker's fee and/or participated in advisory boards from Boehringer Ingelheim, Pfizer, Daiichi Sankyo, and Bayer. He has been a (co-)investigator in clinical trials with reversal agents. Peter Verhamme has received honoraria for lectures and advisory boards from Bayer-Healthcare, Boehringer-Ingelheim, Pfizer, Daiichi-Sankyo, Portola and Bristel-Myers-Squibb and received research support from Bayer-Healthcare, Boehringer-Ingelheim and Daiichi-Sankyo.

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