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IDARUCIZUMAB FOR REVERSAL OF DABIGATRAN IN EARLY/EMERGENCY SURGERIES: A CASE SERIES

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☐ **Abstract—Background: Idarucizumab is a humanized, monoclonal antibody fragment used specifically to reverse the anticoagulant effects of dabigatran. Case Reports: We discuss 4 cases of patients who were treated with idarucizumab to reverse dabigatran before early/emergency surgery. Two of the patients had subdural hematomas, 1 had a splenic laceration, and 1 had Fournier gangrene. All patients received 5 g of idarucizumab before surgery. Intraoperative blood loss in all patients was normal, no adverse events were reported, and the patients recovered normally. Why Should an Emergency Physician be Aware of This?: The case reports presented provide detailed, practical, real-world experience beyond that reported in other case reports and the Reversal Effects of Idarucizumab on Active Dabigatran study. This can help guide clinicians on how idarucizumab can reverse the anticoagulant effect of dabigatran in emergency situations, including patients with subdural hematoma. Our experience suggests that idarucizumab may be a safe and effective antidote to the effects of dabigatran in real-life bleeding situations involving early or emergency surgeries.** © **2019 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).**

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☐ **Keywords—anticoagulation reversal; dabigatran; emergency surgery; idarucizumab; intracerebral hemorrhage; subdural hematoma**

INTRODUCTION

Direct oral anticoagulants (DOACs) have a variety of features that make them suitable alternatives to warfarin (1). Compared with warfarin, all DOACs have a faster onset of action, with shorter time to peak concentration, shorter half-lives, and fewer food and drug interactions (1,2). DOACs can therefore be administered without routine coagulation profile monitoring (3).

The lack of specific antidotes for DOACs was previously a concern, however, and may still present emergency physicians with questions regarding their optimal use. Idarucizumab (Boehringer Ingelheim, Ingelheim am Rhein, Germany) is a specific reversal agent to dabigatran that was approved by the U.S. Food and Drug Administration in October 2015 (4). Idarucizumab is an antibody fragment that binds dabigatran with an affinity approximately 350 times higher than thrombin; it only works to reverse dabigatran and does not work with factor Xa inhibitors or vitamin K antagonists (5). By binding free and thrombin-bound dabigatran, idarucizumab rapidly (within minutes) neutralizes dabigatran's activity (6).

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Results of the prospective Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study demonstrated complete reversal of the anticoagulant effect of dabigatran within minutes of idarucizumab administration (7). Most real-world evidence on use of idarucizumab is focused on its use in patients with acute ischemic stroke (for intravenous [IV] thrombolysis) and in patients needing emergency surgery or procedures (8–30). Other case reports involve the use of idarucizumab in dabigatran overdose, intracerebral hemorrhage (ICH), heart transplantation, and situations of uncontrolled or life-threatening bleeding (Supplementary Video 1) (23,31–39). Nonetheless, because of potential differences in patients' presentations between the RE-VERSE AD study and these case reports, additional real-world data are needed to understand situations prompting idarucizumab use and to guide management in clinical situations. This case series presents our real-world experience with the use of idarucizumab for the reversal of dabigatran in 4 patients who underwent early/emergency surgery.

CASE REPORTS

Cases were retrospectively chosen by the authors or their colleagues based on a patient receiving dabigatran who underwent early/emergency surgery or experienced a subdural hematoma (SDH) and had been treated with idarucizumab.

Case 1: Subdural Hematoma

This patient's history is shown in Table 1.

On the evening of March 23, 2016, the patient noted a moderate headache and came into the emergency department (ED), where the SDH was discovered. There was no trauma. The time of the last dose of dabigatran was unknown but was likely to have occurred on March 23rd because of the patient's elevated partial thromboplastin time (PTT) of 53 seconds at 7:40 PM in the ED. A computed tomography (CT) scan in the ED showed a 19-mm right and 8-mm left SDH, with a 4-mm right-to-left shift (Figure 1).

The patient's Glasgow Coma Scale score in the ED at 7:40 PM was 15, and his National Institutes of Health Stroke Scale score was 0. About 6 hours later, the patient received 2.5 g idarucizumab intravenously at 1:11 AM hours, which was repeated at 1:24 AM on March 24th, with the intent of reversing dabigatran's effect and preventing any further enlargement of the SDH. This resulted in normalization of the coagulation parameters measured at 4:45 AM, such as a shortening of the PTT to 31.8 s. After the patient was stable and the clot was allowed to organize and liquefy, on March 26th right frontal and right parietal burr holes were placed to drain the blood. The patient was in normal sinus rhythm, and no further antithrombotic medications were given. The headache persisted, more on the left. A CT scan on April 7th showed a 13-mm left SDH, with a 5-mm left-to-right shift. On April 16, the patient had a left burr hole placed. A CT scan on May 5 showed a minimal residual SDH.

Case 2: Subdural Hematoma

This patient's history is shown in Table 2.

The patient experienced general worsening for 1 week and stopped speaking on the day of admission. The primary suspicion was fluid imbalance. Five days before admission to a community hospital the patient had fallen in her home.

A teleneurology consultation of a CT scan done at admission showed bilateral SDH, with midline shift and fresh bleeding (Figure 2). Immediate administration of idarucizumab 5 g was recommended, with the patient receiving this 2 h after admission, 30 min after the CT scan.

During neurosurgery in a tertiary care hospital, an acute-on-chronic bilateral SDH was confirmed. A small craniotomy was performed, with hematoma evacuation. The patient's aphasia improved, and she was discharged to a community hospital. She was told to resume dabigatran after 3 weeks, although the date she resumed dabigatran was not documented.

After 3 months, a small chronic SDH, with minimal additional bleeding, without any space-occupying effect, was seen on a CT scan (Figure 3). Although this CT scan

Table 1. Man with Subdural Hematoma: History

Patient	81-year-old Man
History of present illness	Atrial fibrillation discovered in 2011 and placed on dabigatran
Presenting signs	In March 2016, noted moderate headache. No trauma. CT on March 23, 2016 showed a 19-mm right and 8-mm left SDH with a 4-mm right-to-left shift
Coagulation parameters	In ED at 7:40 PM on March 23, 2016: PTT 53 s, PT 18.7 s, and INR 1.53 Idarucizumab 2.5 g IV each given at 1:11 AM and 1:24 AM on March 24, 2016 After idarucizumab administration, at 4:45 AM, PTT 31.8 s, PT 15.1 s, and INR 1.16
Medical history	Transient ischemic attack of decreased speech in 2011
Surgical history	None
Medications	Dabigatran

CT = computed tomography; ED = emergency department; INR = international normalized ratio; IV = intravenous; PT = prothrombin time; PTT = partial thromboplastin time; SDH = subdural hematoma.

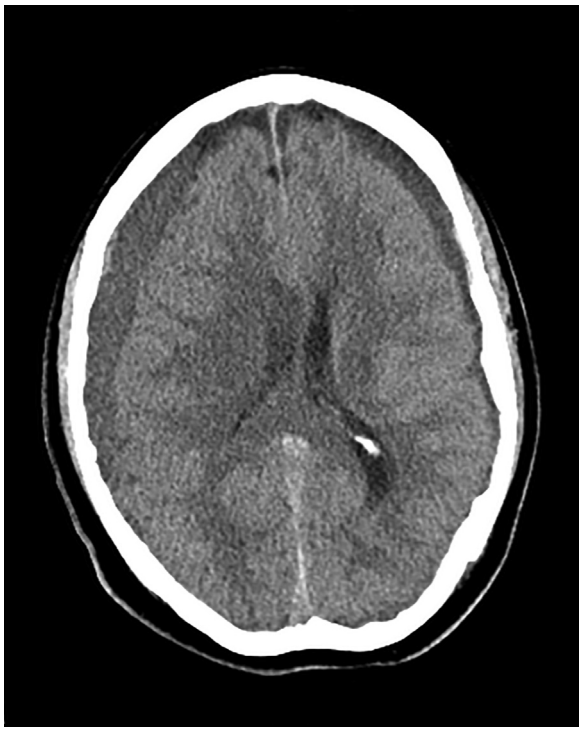

Figure 1. Computed tomography scan on presentation on March 23, 2016, showing bilateral subdural hematomas, 19-mm thick on the right and 8-mm thick on the left, with a 4-mm right-to-left shift.

(Figure 3) appears to show a new left middle cerebral artery (MCA) infarction that was not present on the initial CT scan (Figure 2), the MCA infarction was old, seen on a CT scan in 2010. The patient's symptoms were not documented after the MCA infarction in 2010 up until the SDH in 2017. The patient's last follow-up was after 1 year, during which time she was not receiving an anticoagulant and was living in a nursing home.

Case 3: Splenic Laceration

This patient's history is shown in Table 3.

In the ED, the patient was stable initially, but his abdominal pain worsened, and he progressively became tachycardic (pulse, 118 beats/min) and hypotensive (blood pressure 88/68 mm Hg). He was immediately resuscitated in the ED with 1 L of fluid, and a second liter was started. The patient responded to the fluids but then became hypotensive. According to hospital protocol, 2 units of uncrossed blood were initiated; the patient transiently responded.

In preparation for an emergency exploratory laparotomy, idarucizumab 5 g was ordered in the ED and administered via bolus injection in the operating room, approximately 10 min before beginning the surgery. Two vials of 2.5 g of idarucizumab were consecutively given over a period of ≤1 min each. Coagulation parameters were not assessed at any time. During the surgery, a severe splenic laceration and a mesenteric laceration were confirmed, and an approximately 2 L blood loss was noted. Splenectomy and repair of the mesentery were performed, and 2 units of packed red blood cells and 2 units of fresh frozen plasma were given during the surgery. Intraoperative blood loss was normal.

After the surgery, the patient was transferred to the intensive care unit in a serious but stable condition, where he remained for 3 days. He was extubated on postoperative day (POD) 1, and dabigatran was reinitiated in the intensive care unit on POD 2. The patient was discharged home in stable condition on POD 6. Postsplenectomy immunizations were given at the 2-week follow-up. The patient had a total of 2 follow-up visits, is active, lives independently with his spouse, and has had no long-term issues.

Case 4: Fournier Gangrene

This patient's history is shown in Table 4.

The patient arrived at the ED around 3:00 PM and was taken to the operating room at 6:00 PM. Coagulation parameters were not assessed at any time. Idarucizumab 5 g was administered in the ED via bolus injection just before the patient was emergently transferred to the operating room. He had surgery approximately 45 min after the last idarucizumab dose and underwent a wide radical

Table 2. Woman with Subdural Hematoma: History

Patient	80-year-old Woman	
History of present illness	General worsening for 1 week	
Presenting signs	Aphasia on day of admission	
Coagulation parameters	In ED at admission, INR 1.91; PTT 72.4 s (local reference range 26–40 s); platelets: within reference range; normal GFR At neurosurgery (ie, 1:24 AM; incision made at 7:10 AM), INR 1.31; aPTT 23.1 s (local reference range <35 s)	
Medical history	Atrial fibrillation	Invasive mammary carcinoma
	Left MCA infarction–7 years	Pulmonary embolism–10 months
Medications	Dabigatran 150 mg bid (time of last dose not documented)	

aPTT = activated partial thromboplastin time; bid = twice daily; ED = emergency department; GFR = glomerular filtration rate; INR = international normalized ratio; MCA = middle cerebral artery; PTT = partial thromboplastin time.

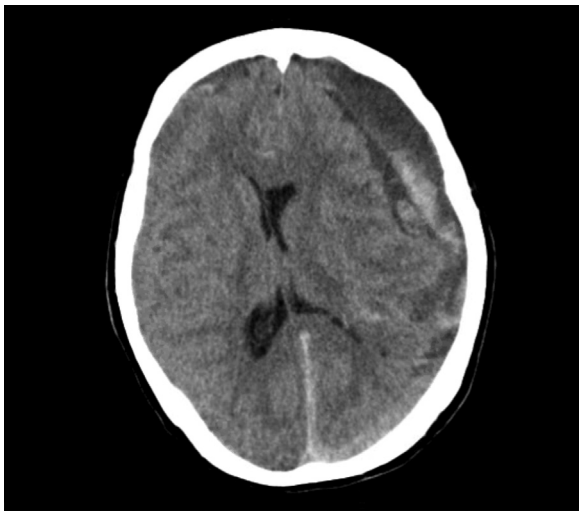

Figure 2. Computed tomography scan on October 26, 2016, showing bilateral subdural hematomas with midline shift and fresh bleeding.

debridement of the scrotum, perineal skin, buttock, and subcutaneous tissue. Intraoperative blood loss was normal.

The patient was admitted to the hospital after the surgery and required repeat wound debridement on PODs 1 and 3. Dabigatran was reinitiated on POD 3, and the patient was discharged to a skilled nursing facility on POD 6. The patient ultimately required an approximately 8- × 8-cm split-thickness skin graft to the perineal/buttock area. Vacuum-assisted closure was used for immediate wound care. The patient was discharged from surgical care and did well, with no long-term complications.

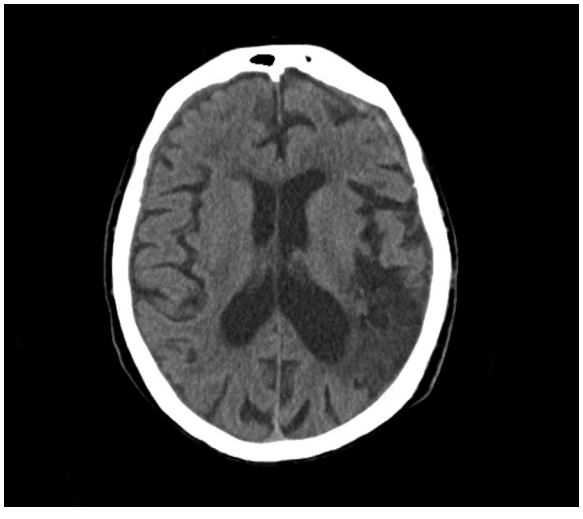

Figure 3. Computed tomography scan on January 25, 2017, showing a small chronic subdural hematoma with minimal additional bleeding, without any space-occupying effect.

Table 3. Man with Splenic Laceration: History

Patient	74-year-old Man
History of present illness	Single-vehicle, roll-over MVA; transported to a level 1 trauma center via aeromedical transportation because of severity of injuries
Presenting signs and symptoms*	Shortness of breath, abdominal pain, seatbelt abrasions, and multiple contusions
Vital signs*	Pulse 92 beats/min, blood pressure 104/76 mm Hg, respiration rate 26 breaths/min; oxygen saturation 92% on 100% nonrebreather mask
Medical history	Hypertension, hypercholesterolemia, COPD, and NVAF
Surgical history	Knee replacement surgery
Medications	Carvedilol, atorvastatin, albuterol, and dabigatran (taken ~8 h before the MVA)
ED testing	CXR: 40% pneumothorax, for which a chest tube was placed; CT scan of head, chest, abdomen, and pelvis: grade 3 splenic laceration, significant hemoperitoneum, and multiple rib fractures
Laboratory findings	Hemoglobin (11.9 g/dL), hematocrit (33.2%); repeat CBC drawn intraoperatively revealed hemoglobin (9.6 g/dL) and hematocrit (30.0%)

CBC = complete blood cell count; COPD = chronic obstructive pulmonary disease; CT = computed tomography; CXR = chest radiograph; ED = emergency department; MVA = motor vehicle accident; NVAF = nonvalvular atrial fibrillation.
* As reported by emergency medical services.

DISCUSSION

The patients' cases presented here offer practical experience to guide clinicians on how idarucizumab can reverse the anticoagulant effect of dabigatran in emergency situations, including in patients with SDH. With the administration of idarucizumab, the estimated intraoperative blood loss was described as normal in all 4 patients. Intraoperative hemostasis was achieved effectively even in the patient with splenic and mesenteric lacerations (case 3), who had a traumatic blood loss of approximately 2 L.

No adverse events were reported in any patient. Although claims of safety or effectiveness cannot be made from these case reports in the absence of further data, the results of idarucizumab demonstrated here appear to be consistent with those of the RE-VERSE AD study, its interim subgroup analysis of 18 patients with ICH, as well as other case studies of idarucizumab use in patients with various conditions involving uncontrollable or life-threatening bleeding (7,23,33,36–40).

The limited real-world experience with idarucizumab in patients with ICH could make clinicians cautious in using idarucizumab. However, successful use of idarucizumab in the patients with SDH presented here, as well as in 2 patients with ICH and a patient with chronic SDH, may

Table 4. Man with Fournier Gangrene: History

Patient	56-year-old Man
History of present illness	Presented to the ED with significant perineal and scrotal discomfort, and a history of irritation in the area for >1 month
Presenting signs in ED	Severe gangrene involving the scrotum, perineal area, and buttock
Vital signs in ED	Pulse 115 beats/min, respiration rate 20 breaths/min, blood pressure 102/74 mm Hg, and oxygen saturation 93% on 4L nasal cannula
Medical history	Poorly controlled T2DM, hypertension, and NVAF
Surgical history	Sinus surgery
Social history	Smoker
Medications	Metformin, metoprolol, lisinopril, and dabigatran (taken ~6 h before coming to the ED)
Laboratory findings	Within reference range: hemoglobin, hematocrit, platelet count, potassium, chloride, PCO_2, and PO_2

ED = emergency department; NVAF = nonvalvular atrial fibrillation; PCO_2 = partial pressure of carbon dioxide; PO_2 = partial pressure of oxygen; T2DM = type 2 diabetes mellitus.

help allay these concerns (33,41). Before the advent of idarucizumab, the management of dabigatran-related ICH included general supportive measures after dabigatran discontinuation, as well as a variety of less than fully effective approaches, such as hemodialysis and 3- or 4-factor prothrombin complex concentrates (42). The use of idarucizumab in patients with ICH can, therefore, offer a more effective and safe approach to reverse the anticoagulant effects of dabigatran in ICH than the previous measures.

Our experience suggests that idarucizumab can be administered per clinical need in the absence of dabigatran measurement and coagulation parameters. Of the 4 patients presented here, coagulation parameters were available for only 2, and dabigatran levels were not assessed for any patient. Ecarin clotting time (ECT) and diluted thrombin time (dTT) tests have been shown to accurately identify dabigatran's effect and were used in the RE-VERSE AD study to assess the complete reversal of dabigatran (7,43). Reasons for not ordering ECT or dTT tests for the 81-year-old man with SDH (case 1) were not recorded, but it is common that these assays are not available in many institutions. However, although PTT is a reasonable measure of dabigatran activity, the relationship between PTT and dabigatran's effect is not linear over the clinically used dabigatran concentrations (44). By contrast, ECT and dTT show a linear relationship and strong correlation with dabigatran's effect (43). Prothrombin time is not recommended because of its insensitivity to dabigatran's effects (44) (Supplementary Video 2). In the patient with SDH (case 1), idarucizumab was not used to allow early/emergency surgery but rather to limit further bleeding and for clinical stabilization in the preparation for elective clot drainage.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Idarucizumab is a humanized, monoclonal antibody that is approved by the U.S. Food and Drug Administration and that specifically reverses the anticoagulant effect of dabigatran. Real-world evidence on idarucizumab use mainly focuses on patients with acute ischemic stroke, ICH, heart transplantation, and uncontrolled bleeding. A set protocol is important for idarucizumab administration so that other members of the health care team in the ED are also aware (Supplementary Video 3). As patients' presentations differ from those in the RE-VERSE AD study, further real-world data are needed to understand situations prompting idarucizumab use and to guide management in clinical situations, such as in patients presenting with splenic laceration, Fournier gangrene, and SDH. These case reports indicate that idarucizumab is effective and safe and that it provides rapid reversal of the anticoagulant effect of dabigatran. Data also suggest that idarucizumab could be administered safely per patient need in the absence of the measurement of dabigatran and coagulation parameters, although this should be regarded as an exception. These results are consistent with the results of the RE-VERSE AD study and could help allay the fears of emergency physicians, especially in patients with ICH.

Our real-life experience with these 4 patients, including 2 with SDH, confirms the clinical trial results that idarucizumab appears to be an effective and safe option for the reversal of the anticoagulant action of dabigatran in early or emergency surgical situations. Large prospective cohort studies or registry studies are needed to confirm effectiveness and safety of idarucizumab in real-life settings.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jemermed.2019.09.038.