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Case Report

Spontaneous acute subdural hematoma due to fondaparinux: Report of two cases

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Abstract

Background: Spontaneous acute subdural hematomas (SDHs) are rare. Risk factors for development of these hematomas include conditions such as hypertension, vascular abnormalities such as aneurysm or arteriovenous malformation, or consumption of anticoagulants.

Case Description: Here, the authors report two patients who suffered from spontaneous acute SDH while taking fondaparinux for venous thromboembolism prophylaxis. One patient suffered from a remote episode of traumatic brain injury and underwent a decompressive craniectomy 3 weeks prior to presentation, whereas the other patient had been self-medicating with aspirin.

Conclusion: To our knowledge, these two patients illustrate the first cases of spontaneous acute SDH formation most likely attributed to consumption of fondaparinux.

Key Words: Acute subdural hematoma, decompressive craniectomy, fondaparinux, venous thromboembolism prophylaxis

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INTRODUCTION

Acute subdural hematomas (SDHs) are frequently due to injury to cerebral bridging veins secondary to head trauma.[1,33] Spontaneous acute SDH is rare. The reported incidences of spontaneous acute SDHs relative to total acute SDHs have ranged from 2 to 6.7%.[13,20,29,35] Conditions associated with development of spontaneous acute SDH include hypertension,[22] aneurysms,[17,19] arterio-venous malformations,[25] and cocaine usage.[5,18,28] Pharmacologic therapy linked with the development of spontaneous acute SDH includes aspirin,[13,24] heparin,[13] and warfarin.[4,13,26,32] Other reports of spontaneous acute SDH mention risk factors such as coagulopathies related to coagulation factor deficiencies[3,7,33] and immune thrombocytopenic purpura.[27]

Here, we report two patients who suffered from spontaneous acute SDH while taking fondaparinux for venous thromboembolism (VTE) prophylaxis. One patient suffered from a remote episode of traumatic brain injury and underwent decompressive craniectomy 3 weeks prior to presentation, whereas the other patient had been self-medicating with aspirin. A literature review will underscore these two cases, with a focus on the risk of fondaparinux for causing spontaneous intracranial hemorrhage during VTE prophylaxis.

CASE REPORTS

Patient 1

A 33-year-old male suffered a severe traumatic brain injury after a motorcycle accident. He underwent evacuation of a left epidural hematoma and subsequently a decompressive craniectomy. He improved to a Glascow Coma Scale (GCS) 11 (E4M5V2) and was transferred to rehabilitation 3 weeks after the accident. During his rehabilitation, the patient was started on fondaparinux for VTE prophylaxis. Several days into the course of his rehabilitation, the patient developed a sudden decrease in his mental status without any trauma. An emergent head computed tomography (CT) showed a new acute SDH with a midline shift [Figure 1a, b] The patient was immediately taken to the operating room, a ventriculostomy catheter was placed, and the subgaleal and the subdural hematomas were evacuated [Figure 1c, d]. The patient returned to his baseline neurologic status within days and continued his rehabilitation.

Patient 2

A 34-year-old Burmese male presented to the Emergency Room with intractable headaches. The patient had a history of polycythemia vera and had been recently started on fondaparinux for thromboembolism prophylaxis. On the day of admission, he also took aspirin to relieve his headaches. His neurologic examination was non-focal. A head CT showed a 2.2-cm left frontal acute SDH [Figure 2a]. He received platelet transfusion and underwent an urgent hematoma evacuation [Figure 2b]. His use of fondaparinux medication was not made known to us until the following day. On the follow-up CT scan [Figure 2c], he developed a recurrent subdural hemorrhage and required a repeat evacuation within 24 hours of the initial surgery. He received fresh frozen plasma and platelets preoperatively; intraoperative hemostasis was obtained using Gel foam powder and thrombin. He recovered gradually and was discharged neurologically intact after a short course of rehabilitation.

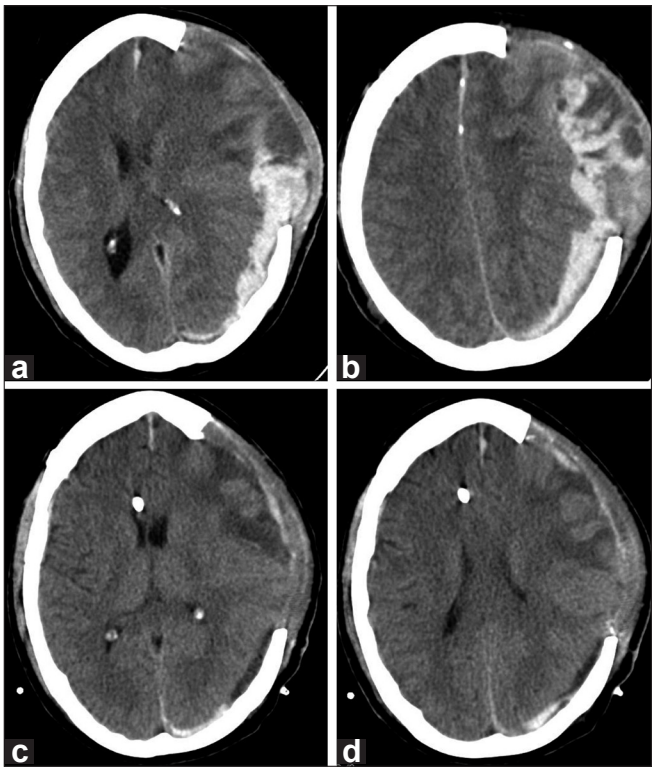

Figure 1: Several days into the course of his rehabilitation, patient 1 developed a sudden decrease in his mental status without any trauma. An emergent head CT showed a new acute SDH with a midline shift (a and b). The patient was immediately taken to the operating room, a ventriculostomy catheter was placed, and the subgaleal and the subdural hematomas were evacuated (c and d)

DISCUSSION

Spontaneous acute SDH is a rare but serious condition. Mortality rate has been reported to be between 60 and 76.5%.[6,22] Early surgical intervention is often imperative for hematomas with significant mass effect. The survival rate for surgery within 4 hours of acute onset compared to surgery after 4 hours is 50 to 0%, respectively.[22] Other favorable variables include a high GCS score upon admission, appropriate pupillary reactivity, and young age.[22]

The term "spontaneous acute SDH" has been used rather indiscriminately in the literature. Some authors[22,23] use the term strictly to refer to subdural hematomas caused by the rupture of a cortical vessel that does not involve a cerebral aneurysm, arterio-venous malformation, tumor, metastasis, or blood dyscrasias. Other authors[7,13,19,24,33,34] have used the term based simply on the absence of a traumatic history. We prefer to use the term according to the latter definition. Head trauma was not an immediate factor in the development of SDH in either of the authors' patients. Patient 1 was recovering from a decompressive craniectomy that had occurred 3 weeks earlier. There was no history of any trauma for the second patient. Aggravating cofactors existing in these two patients included self-medication with a platelet inhibitor in the second patient. No cerebrovascular abnormality was observed in either case during surgery.

Both the patients experienced a spontaneous acute SDH after recently taking fondaparinux for VTE prophylaxis. There has been one report of an SDH resulting from a fall while a patient was taking fondaparinux.[10] Another report linked a large spontaneous retroperitoneal hematoma to this pharmacologic agent.[15] To our knowledge, our report presents the first instances of spontaneous acute SDH most likely attributed to fondaparinux. The second patient had also been taking aspirin, but the influence of this on the development of spontaneous hemorrhage cannot be fully assessed. However, the recent introduction

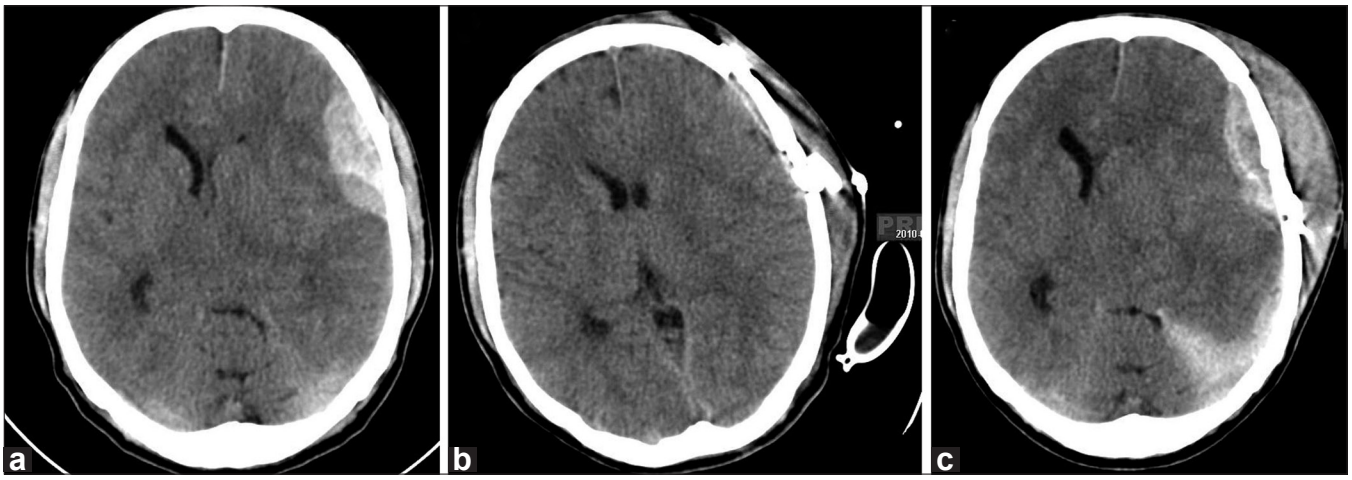

Figure 2: For patient 2, on admission, a head CT showed a 2.2-cm left frontal acute SDH (a) He received platelet transfusion and underwent an urgent hematoma evacuation (b) His use of fondaparinux medication was not made known to us until the following day. A follow-up CT scan (c) showed that he had developed a recurrent subdural hemorrhage, and he required a repeat evacuation within 24 hours of the initial surgery

of fondaparinux in this patient's drug regimen suggested that this drug was the trigger, either as an independent factor or in a combined mechanism with aspirin.

Fondaparinux acts as a selective AT-III dependent inhibitor of activated factor Xa.[8] The drug is approved by the Food and Drug Administration for VTE prophylaxis after hip fracture surgery, total hip replacement, total knee replacement, and major abdominal surgery.[8] Moreover, it is approved for the initial management of deep venous thrombosis (DVT) and pulmonary embolism.[8] However, the drug is contraindicated in patients with renal failure (creatinine clearance <30 ml/min), body weight <50 kg, active major bleeding, and bacterial endocarditis.

Although its safety has been shown in previous studies when compared to low-molecular-weight heparin (LMWH), a black box warning has been issued for its use near the neural axis, describing the potential for development of epidural hematomas. During the Phase III trials of fondaparinux, the patients who underwent surgical procedures involving brain and spine in the last 3 months were excluded from the study. There is no specific antidote available to counteract the effects of fondaparinux. However, in cases of severe bleeding, the anticoagulant effect can be reversed with fresh frozen plasma or recombinant factor VIIa.

The occurrences of spontaneous hematomas and the subsequent re-hemorrhage in our second patient echo the potential risks of major bleeding while taking medications for pharmacologic VTE prophylaxis. Unfortunately, no controlled trials have focused on VTE prophylaxis for the neurosurgical population. Established in 2004, the present guidelines for neurosurgical procedures were extrapolated from data for general surgery and orthopedic surgery; the recommendations embraced multimodal prophylaxis with mechanical methods, which could be enhanced by either LMWH or unfractionated heparin (UFH).[11,16] There are no guidelines for the use of fondaparinux in neurosurgery. Since that time, several articles[2,12] have emerged stressing the increased risk of intracranial hemorrhage for patients receiving LMWH prophylaxis compared with the patients receiving mechanical modalities. Surprisingly, a meta-analysis by Collen *et al.*[11] suggested that mechanical modalities (i.e., intermittent compression devices) may be as effective as heparin therapy in the neurosurgical population without the hemorrhagic risks. This is contrary to popular belief that pharmacologic therapy is considered superior for prevention of thromboembolism.[11]

The selectivity and long half-life of fondaparinux made the drug an appealing possibility for VTE prophylaxis.[8] A meta-analysis[31] of four multicenter, prospective, randomized controlled trials[9,14,21,30] involving orthopedic procedures showed that fondaparinux had a lower incidence of VTE compared with enoxaparin, but had more episodes of bleeding leading to re-operation and/or bleeding with high index (a measure of blood transfusions required). No episodes of major intraspinal or intracranial bleeding occurred during these trials. However, the studies excluded patients with a hemorrhagic stroke within the previous 3 months; patients with a brain, spinal, or ophthalmologic surgery within the previous 3 months; patients whose surgery required an indwelling, intrathecal, or epidural catheter during the study; and patients with difficulty achieving epidural or spinal anesthesia.

CONCLUSIONS

Fondaparinux may be associated with an increased rate of

intracranial hemorrhage. Its use for neurosurgical patients should be exercised with caution.

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