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Fondaparinux in a critically Ill patient with heparin-induced thrombocytopenia
A case report

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Abstract

Rationale: Fondaparinux, as a factor Xa-inhibitor, is used off label to manage heparin-induced thrombocytopenia (HIT), but little experience with HIT patients has been reported in the literature. Moreover, the use of fondaparinux for full anticoagulation in critically ill patients with HIT and renal insufficiency is limited.

Patient concerns: A trauma patient, who had received low molecular weight heparin (LMWH) and heparin to treat venous thromboembolism, developed thrombocytopenia and multiple organ dysfunction in the intensive care unit (ICU). Also, her deep venous thromboembolism (DVT) continued to progress.

Diagnosis: The final diagnosis was HIT.

Interventions: Fondaparinux was temporarily used for anticoagulation treatment of DVT for 7 days when another anticoagulant (argatroban) was unavailable. Although the patient had kidney dysfunction, a full therapeutic dose of 7.5 mg fondaparinux was administered every morning through subcutaneous injection for consecutive 7 days.

Outcomes: The patient's thrombocytopenia and thrombosis were successfully treated without bleeding complications during therapeutic fondaparinux administration.

Lessons: This is the first case reporting the successful use of fondaparinux for full anticoagulation for DVT in a critically ill patient with HIT and renal insufficiency. Our experience suggests that fondaparinux might be an alternative for anticoagulation treatment in patients with HIT and kidney dysfunction if another anticoagulant (argatroban) is unavailable.

Abbreviations: aPTT = activated partial thromboplastin time, BNP = brain natriuretic peptide, DIC = disseminated intravascular coagulation, DVT = deep venous thrombosis, eGFR = estimated glomerular filtration rate, FFP = fresh frozen plasma, HIT = heparin-induced thrombocytopenia, ICU = intensive care unit, ISTH = International Society on Thrombosis and Haemastasis, LMWH = low molecular weight heparin, PFNA = proximal femoral nail antirotation, PT = prothrombin time.

Keywords: fondaparinux, heparin induced thrombocytopenia, renal insufficiency, therapeutic dose

1. Introduction

Heparin-induced thrombocytopenia (HIT) is one potential cause of thrombocytopenia in intensive care unit (ICU). Moreover, patients admitted to the ICU are exposed to heparin when they require prophylaxis and treatment for thromboembolism, anti-coagulation therapy, and catheter rinsing.[1] One study reported that the incidence rate of HIT was <1% in the ICU, but it can be occult and life threatening in clinical practice.[2] Direct thrombin inhibitors, such as argatroban and lepirudin, have been approved to treat HIT, but fondaparinux has not been approved.[3] However, fondaparinux has gained attention for its used in the treatment and prophylaxis of thromboembolism in HIT.[4–7] Furthermore, experience is limited with the application of fondaparinux for full anticoagulation in critically ill patients with HIT and renal insufficiency.

Here, we report the case of a trauma patient who, after receiving low molecular weight heparin (LMWH)/heparin and developed multiple organ dysfunction and HIT, was managed successfully by full-dose fondaparinux for thromboembolism anticoagulation without bleeding complications.

2. Case description

An 80-year-old woman with a history of hypertension, diabetes, atrial fibrillation, and cerebral infarction had a right intertro-
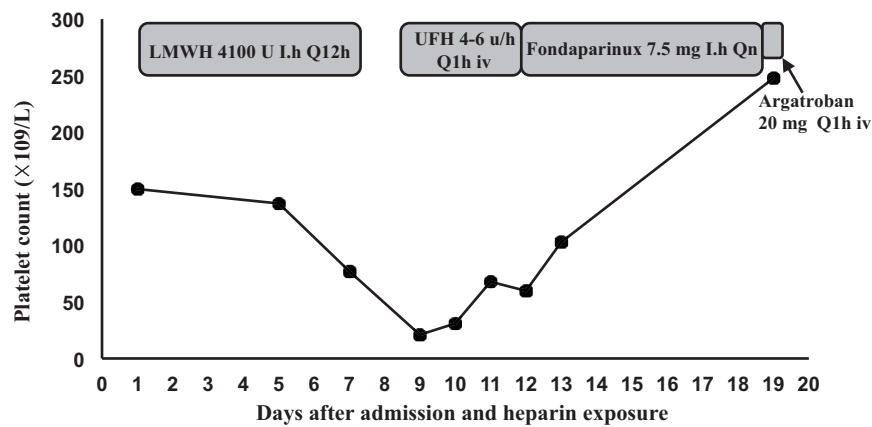
Figure 1. Schematic presentation of platelet count and anticoagulation management.

chanteric and right humeral fracture. She had the following characteristics: blood pressure 182/105 mm Hg, pulse 135/min, temperature 36.5°C, and respiratory rate 20/min. A physical examination revealed obvious swelling and ecchymosis of the right extremities with tenderness. When she was admitted, laboratory tests revealed the following: hemoglobin 113 g/L, platelet count 150×10^9/L, D-dimer 3.42 mg/LFEU, prothrombin time (PT) 12.0 seconds, activated partial thromboplastin time (aPTT) 23.9 s, fibrinogen 2.07 g/L, T-troponin 0.556 μg/L, brain natriuretic peptide (BNP) 3028 ng/L, and plasma creatinine 84 μmol/L. Ultrasonography showed the susceptible presence of thrombus in the intramuscular veins of the right leg. LMWH was administered for the susceptible thrombus at an empirical dose (4100 U q12h) from day 1 to day 6 because the patient could not be weighed (Fig. 1).

On day 7, the patient underwent closed reduction and proximal femoral nail antirotation (PFNA) fixation of the intertrochanteric fracture of the femur. Blood loss of <30 mL occurred during the surgery. Due to the increased aPTT (48.8 seconds) before surgery, 200 mL of fresh frozen plasma (FFP) was transfused. Heparin was used to replace the LMWH for anticoagulation (Fig. 1). A significant decrease in the platelet

count was observed on day 7 when the patient was transferred to the ICU after the operation (platelet count 43×10^9/L after surgery). The platelet count had decreased from 150 to 77×10^9/L before surgery. Moreover, her hemoglobin decreased from 113 to 81 g/L after surgery. The nadir of the platelet count occurred on day 8, at 21×10^9/L, and then the platelet count was maintained at 31 to 46×10^9/L (Fig. 1). Simultaneously, her hemoglobin level was maintained at approximately 80 g/L. Cranial CT and abdominal ultrasonography excluded obvious bleeding in those high-risk areas. Additionally, the patient's D-dimer level increased from 3.42 to 9.88 mg/LFEU, and the fibrinogen level decreased from 2.07 to 1.50 g/L after surgery. Compared to the preoperative condition, the thromboembolism worsened, even with anticoagulation treatment. Ultrasonography detected deep venous thromboembolism (DVT) and intramuscular thrombus formation in both legs and the left arm. Additionally, skin necrosis was observed on the toes. Many risk factors and similar clinical manifestations of disseminated intravascular coagulation (DIC) were present (low platelet and fibrinogen levels and a high D-dimer level), and DIC was initially suspected. However, when treatment for DIC was administered, including intermittent platelet and FFP transfusion, the condition

Table 1
Clinical information and treatment timeline.

Day after admission	1	5	7 (Surgery)	9	10	11	12	13	19
Heparin exposure	LMWH until day 7	LMWH until day 7		UFH	UFH	Stop UFH			
Other management				Plt transfusion	Plt transfusion		Fondaparinux until day 18	Fondaparinux until day 18	Argatroban
Thrombosis					Ultrasonography: venous thrombosis		Acral necrosis	Acral necrosis	Acral necrosis
Plt/10^9/L (100–350)	150	137	77–43	21–46	31–35	68	60–67	103	248
Hbg/L (120–160)	113	—	91–81	77–79	79–95	98–89	90–81	84	96
eGFR/mL/min/1.73 m²	57	68	82	72	82	58	43	37	25
PT/s (10–12) (10.4–12.6)	12.0	—	12.3–12.9	14.0–14.0	13.3–13.8	13.4–13.6	14.2–13.8	13.9	27.6
aPTT/s (22.7–31.8)	23.9	—	48.8–49.4	49.8–50.4	43.9–46.4	41.4–44.5	47.2–38.6	37.4	118.8
D-dimer mg/LFEU (0–0.55)	3.42	—	9.63–9.88	62.45–63.32	78.46–90.66	68.69–101.55	85.85–61.31	21.17	7.42
Fbg g/L (1.80–3.50)	2.07	—	1.50–1.29	1.15–1.35	1.18–1.07	1.28–1.35	0.79–1.44	1.69	4.96

aPTT = activated partial thromboplastin time, Fbg = fibrinogen, Hbg = hemoglobin, LMWH = low molecular heparin, Plt = platelets, PT = prothrombin time, UFH = unfractionated heparin.
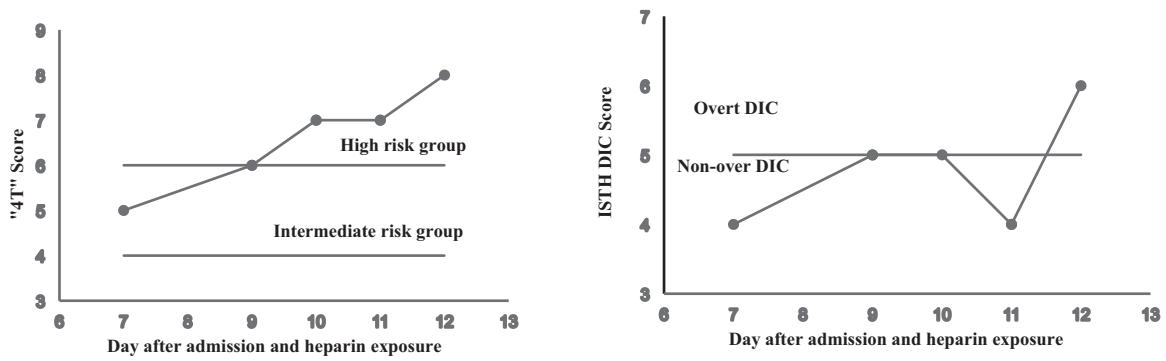
Figure 2. Schematic presentation of "4T" and ISTH DIC scores in the patient. DIC=disseminated intravascular coagulation, ISTH=International Society on Thrombosis and Haemastasis.

worsened. The platelet count was persistently low as shown in Figure 1 (from 31 to 46×10^9/L), the aPTT and PT remained elongated, and the D-dimer level increased to 101.55 mg/LFEU. The timeline of the clinical information and treatment is shown in Table 1. Considering the severe thrombocytopenia, progressive thrombosis, and the timeline of thrombocytopenia after the use of LMWH and heparin, HIT was diagnosed in this patient. Both the International Society on Thrombosis and Haemostasis (ISTH) DIC score and the "4T" score were used to evaluate DIC and HIT.[8,9] The DCI score is classified as follows: ≥5 compatible with overt DIC, repeat score daily; <5 suggestive of nonovert DIC, repeat during the next 1 to 2 days. The "4T" score is classified as follows: 0 to 3 low risk, 4 to 5 intermediate risk, 6 to 8 high risk. The daily ISTH DIC score and "4T" score during the therapeutic periods are shown in Figure 2. Heparin was immediately replaced with fondaparinux due to a shortage of argatroban, and at a dose of 7.5 mg qd through subcutaneous injection. The patient developed multiple organ dysfunction (lung failure requiring a mechanical ventilator, mild liver impairment, and kidney dysfunction). At that point, the plasma creatinine level had increased to 149 μmol/L, and the estimated glomerular filtration rate (eGFR) was 43 mL/min/1.73 m^2 according to the CDK-EPI equation. Her eGFR decreased further to 25 mL/min/1.73 m^2, which was a contraindication for fondaparinux use. The changes in the patient's eGFR are summarized in Figure 3. The platelet count dramatically recovered to 103×10^9/L the next day, and her D-dimer level decreased after fondaparinux was administered (Fig. 1). Due to the high risk of bleeding, we monitored her hemoglobin closely. Surprisingly, the patient's hemoglobin recovered slightly to 90 g/L. Fondaparinux was replaced with argatroban when argatroban was available on day 19. And argatroban was pumped intravenously at a total dose of 20 mg for 2 to 4 hours once a day. Her platelet count reached 248×10^9/L, and no bleeding was observed. Interestingly, her aPTT was prolonged from 43.3 to 118.8 s when argatroban was administered. An overly long aPTT might result from coagulation factor depletion or the dysfunction of argatroban metabolism due to liver impairment. For personal reasons, the patient's family withdrew the patient's treatment and left our hospital on day 19 after the platelet level had fully recovered.
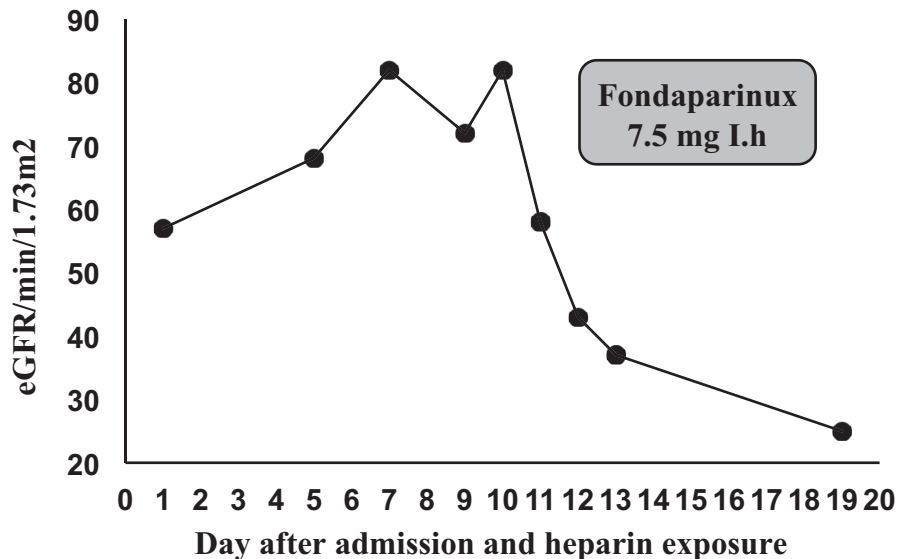

Figure 3. Schematic presentation of eGFR according to the CKD-EPI equation. CKD-EPI = chronic kidney disease-epidemiology collaboration equation, eGFR = estimated glomerular filtration rate.

3. Discussion

Our report describes a rare and successful experience with fondaparinux use for full anticoagulation in a HIT patient with renal insufficiency. To our knowledge, this is the first case regarding fondaparinux use in this specific and susceptible population. This case provides insight into the use of fondaparinux for coagulation in critically ill HIT patients with renal dysfunction.

HIT can be divided into 2 types. Type I is nonimmune-mediated with rapid onset (first 2 days) but with mild thrombocytopenia, and it is self-limited. Type II is mediated by an anti-PF4/heparin antibody and is more commonly observed. In our case, the patient had numerous risk factors for HIT, such as being an elderly female, having major trauma, undergoing orthopedic surgery, being in a hypercoagulable state based on her medical history, and receiving LMWH/heparin.[10] The patient's platelets decreased by approximately 75% on the 7th day after exposure to LMWH, and the DVT further developed even though coagulation continued after the operation. Hence, we suggest that both LMWH and heparin could cause HIT in this case. Moreover, our experience indicates that use of a single timepoint of the ISTH DIC score might incorrectly lead to the identification of HIT in critically ill patients. Hence, we emphasize the combination of the ISTH DIC score and the "4T" score in critically ill patients, and a dynamic evaluation might provide an early warning of HIT.

Fondaparinux is a synthetic, ultralow molecular weight, highly sulfated pentasaccharide that inhibits activated factor X. Fondaparinux does not bind to PF4; therefore, it rarely leads to cross-linked activity with HIT antibodies and does not require routine monitoring. Fondaparinux may be an ideal anticoagulant for managing HIT. However, it has not been approved by the FDA for managing suspected or confirmed acute HIT.[11] Moreover, fondaparinux has a long half-life and it is not recommended for patients with kidney dysfunction concerning increasing bleeding risk due to decreased excretion from kidney.[4] However, a recent study found that fondaparinux might be safe and efficient for patients with renal failure. Mahieu et al[12] reported that fondaparinux was used safely and provided adequate anticoagulation for hemodiafiltration in 4 patients with HIT. Moreover, Cegarra-Sanmartín et al[13] also found that fondaparinux might be a good alternative to heparin based on 15 patients with HIT who presented with renal failure and required continuous renal replacement therapy. Daily monitoring of anti-Xa activity was recommended for the dose titration of fondaparinux in patients with renal failure.[12,13] However, it is only proved in patients undergoing hemodialysis and has not been a routine monitoring method. Because the DVT continued to progress and the other anticoagulant was unavailable, fondaparinux was used for full anticoagulation at a therapeutic dose of 7.5 mg qd for 7 days in this case. Furthermore, fondaparinux has been suggested for anticoagulation in acute coronary syndromes if the glomerular filtration rate is more than 20 mL/min, and the maximum therapeutic period is 8 days.[14] The lowest eGFR was 25 mL/min in this patient; therefore, the application of fondaparinux seems reasonable. Thrombocytopenia is common in critically ill patients with extracorporeal life support due to mechanical damage.[15] But we still should be cautious with presence of HIT in these patients resulting from heparin usage. Recently, Ozturk et al[16] showed a successful case of fondaparinux use for anticoagulation in a patient with HIT on extracorporeal life support. In contrast, another study reported failure of fondaparinux for anticoagulation in a patient with HIT.[17] Therefore, clinical trials are required to validate the safety and efficacy of fondaparinux use for anticoagulation in the management of HIT.

4. Conclusion

In summary, our experience suggests that fondaparinux might be a temporary alternative for anticoagulation of DVT in patients with HIT with kidney dysfunction when another anticoagulant (argatroban) is unavailable.

Author contributions

Supervision: Huaiwu He, Dawei Liu, Yun Long.
Writing – original draft: Yumiao He.
Writing – review & editing: Huaiwu He, Yun Long, Longxiang Su, Wei Cheng.

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