

## CASE REPORTS

# Fondaparinux Treatment in a Neonate with Heparin Induced Thrombocytopenia during Extracorporeal Life Support

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## ABSTRACT

The utilization of mechanical life support due to respiratory insufficiency and serious cardiac pathologies have been increasing. Anticoagulation to prevent clot formation is mandatory and unfractionated heparin is the standard therapy in use. But rarely heparin induced thrombocytopenia (HIT) might develop as an immunologic side effect of heparin. Development of thrombosis as a result of HIT increases the morbidity and mortality. We present a neonate with HIT treated successfully with fondaparinux under extracorporeal life support.

**Keywords:** extracorporeal life support, heparin induced thrombocytopenia, newborn, fondaparinux

## INTRODUCTION

Heparin is the standard anticoagulation therapy in extracorporeal life support (ECLS) due to rapid effect, safety, and rapid reversibility of its effects (1). Heparin induced thrombocytopenia (HIT), is an important problem presenting with thrombocytopenia and thrombosis developed by antibody me-

diated thrombocyte activation and thrombocyte consumption due to immunologic side effect of heparin. These patients have high morbidity and mortality due to thrombotic complications (2).

Alternative anticoagulation instead of heparin is needed in cases with HIT, heparin resistance and in patients with evidence of important thrombosis (3). But there is limited data

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about alternative anticoagulation in patients during ECLS.

We present a treatment with fondaparinux in a neonate whom developed HIT under ECLS after congenital heart surgery. □

### CASE REPORT

A six-day-old male patient was admitted to the hospital with cyanosis during crying. His weight was 3 kg and height 53 cm. He was cyanotic, with an oxygen saturation of 80 % and heart rate was 136 beats/min. His blood pressure was 65/30 mmHg, he had dyspnea and tachypnea. There was cardiomegaly similar to “lying egg” and right ventricular hypertrophy on 12 channel electrocardiography (ECG). Echocardiography revealed the transposition of great arteries. He was intubated, PGE1 and milrinone were initiated. He was operated in the 8th day postnatally but he could not be weaned from cardiopulmonary bypass and he was admitted to the ICU with ECLS. The ECLS circuit consisted of a Deltastream® DP3 diagonal pump head (Medos Medizin technik AG, Stolberg, Germany), a Hilite® polymethylpentene diffusion membrane oxygenator (Medos-Medizintechnik AG, Stolberg, Germany), and Rheoparin coated tubing (MedosMedizintechnik AG, Stolberg, Germany) for both arterial and venous lines. The system is controlled with MDC console, which also includes valuable safety mechanisms, such as a flow sensor with an integrated bubble detector, backflow detection, and temperature sensors. The combined heater-cooler device Deltastream® HC (MedosMedizintechnik AG, Stolberg, Germany) was used to regulate the patients’ temperature. A 8 Fr thin-walled polyurethane DLP arterial cannula (Medtronic, Minneapolis, MN, US) and 14 Fr DLP venous cannula with angled and beveled metal multiport tips (Medtronic corp, Minneapolis, MN, USA) were used. A special cone sized tubing, measuring from 3/8 to 1/4 inches, is connected to the 1/4 oxygenator and 3/8 pump connector.

Milrinone (0.5 mcg/kg/minute) and adrenalin (0.05 mcg/kg/minute) were initiated for inotropic support. Heparin infusion was initiated after control of bleeding and titrated at a level adequate to keep activated clotting time (ACT) between 180-220 seconds. The ECLS settings were adjusted according to the echocardiographic and hemodynamic data. Hemo-

gram and blood chemistry were tested daily. Blood and blood product support were given to keep hematocrit >35%, thrombocyte >100000/mcL, aPTT <80 seconds. The thrombocyte count of 220000 at postoperative day 1, decreased to 20000 at the postoperative day 5. The purplish discoloration started at the peripheral extremities at the postoperative day 6 and spread into cutaneous necrosis in 6 hours (Figure 1a). The cultures for septicemia etiology were sterile. The heparin infusion stopped and heparin in all intravenous treatment fluids were removed. The patient had the score of 7 according to the 4 T scoring system (6-8 high probability) and heparin induced thrombocytopenia was diagnoses indirectly (4,5). Daily subcutaneous 0.2 mg/kg fondaparinux (arixtra®, GlaxoSmithKline) was initiated. The anti-Xa factor level was stabilized at 0.6-1 U/ml.

At the 4<sup>th</sup> day of fondaparinux treatment (postoperative 10<sup>th</sup> day) echocardiographic study revealed a shortening fraction of 28% and the ECLS support was ended. The thrombocyte count increased to 100000 and 250000 at the postoperative day 9 and day 12, respectively. D-dimer level did not increase significantly. There were no hemolysis. The widespread skin necrosis on extremities regressed at the postoperative day 15 but amputation of the left hand at the level of proximal phalanges was needed (Figure 1b). Fondaparinux ceased at the postoperative day 24 and the patient was discharged from hospital at the postoperative day 48. There was no clinical problem after 6 months of follow up. □

### DISCUSSION

Thrombocytopenia is a laboratory finding of the critical illnesses. Although sepsis and



**FIGURE 1.** A) Postoperative day 6 skin necrosis shown in patient. B) Postoperative day 15 amputation of the left hand at the level of proximal phalanges was needed.

hemodilution are the most common causes of thrombocytopenia, HIT must be considered in differential diagnosis especially in patients with heparin treatment. HIT is characterized immunologically by thrombocytopenia and thromboembolic events developed by a series of immunologic effects like platelet activation and aggregation, endothelial activation and thrombin regulation developed as a result of an interaction of heparin IgG antibodies with the complex of thrombocyte factor 4 (PF4). Although it is affected by the type and duration of heparin and the aim of the therapy, the frequency of HIT is 0.7-5% in standard heparin and <1% in low molecular weight heparin therapy (4-5). HIT usually develops 5-10 days after the contact with heparin. This period might be shorter if a previous administration was present, so close follow-up of thrombocyte count may help the detection of the development of HIT (3-5). Various serological tests like PF4/heparin enzyme immune test (PF4/heparin EIA), were in use in diagnosis of HIT. The specificity of these tests were low but due to their high negative predictive values, they are valuable in exclusion of the diagnosis. Serotonin release assay is the gold standard in diagnosis. The most important disadvantage of these tests is the shortage of availability of them. This was the reason of lack of data about these tests in our patient. Because of this, 4T scoring system including the clinic and basic hemogram measurement is widely in use (Table 1). 4T scoring system depends on the basis of grouping HIT probability as low (0-3 points), medium (4-5 points), high (6-8 points) risk by scoring each of the four parameters by 0, 1 and 2 points (4-5). In the present case the serological tests could not be performed but treatment was planned

for a high risk patient as he had 7 points according to the 4T scoring system (he got 2 points from thrombocytopenia, the appearance of thrombocytopenia and the presence of thrombosis and 1 point from the presence of other factors that lead to thrombocytopenia) and was considered high risk.

ECLS has been in use frequently in pediatric cardiac intensive care units. Anticoagulation is mandatory to prevent the coagulation of the blood circulating in this system and the development of bleeding or thromboembolism as a result of the balance between coagulation and anticoagulation is an important problem. Another problem is the absence of an ideal anticoagulant agent and a gold standard test to titrate this agent although the ECLS has been in use more than a period of 30 years (1,6). However, heparin is the most frequently used agent in many of the centers.

Bembea et al reported the data of registered 117 centers of ELSO, and standard heparin has been used in 92% of the cases and the dosage was titrated to keep ACT 180-220 sec. In another study, standard heparin usage in ECLS patients was reported at a dosage titrated to keep aPTT around 1.5-2 times of the normal (7). We used heparin at a dosage titrated to keep ACT around 180-220 sec and confirmed the ACT results with aPTT in the present case.

If HIT develops during ECLS support, heparin treatment should immediately be ceased and alternative anticoagulant drugs should be initiated because 30-50 % thrombosis in different parts of the body was reported even though the heparin treatment was ceased. HIT is a hypercoagulation where thrombin is increased and the aim of the treatment is to prevent the development of thrombin. Direct thrombin in-

| Category                          | 2 points                                                           | 1 point                                                                                | 0 point                        |
|-----------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------|
| Thrombocytopenia                  | >50% decrease<br>20-100 k/L nadir                                  | 30%-50% decrease<br>10-20 k/L nadir                                                    | ≤30% decrease<br>≤10 k/L nadir |
| Timing                            | Onset 5-10 days<br>Onset <1 day (if heparin exposure within 100 d) | Onset ≥10 days<br>Timing or heparin exposure not clear                                 | Onset ≤4 days                  |
| Thrombosis                        | New thrombosis<br>Skin necrosis; Acute systemic reaction           | Progressive or recurrent thrombosis<br>Erythematous skin lesions; suspected thrombosis | None                           |
| Other causes for thrombocytopenia | No other cause                                                     | Possible other cause                                                                   | Definitive other cause         |

**TABLE 1.** 4T score for pretest probability of Heparin induced thrombocytopenia.

Score of 0-3 indicates low probability; 4-5, intermediate probability; and 6-8, high probability.

hibitors (DTI); argatroban, lepirudin, bivalirudin or indirect factor Xa inhibitors; danaparoid and fondaparinux have been in use for HIT treatment (3).

Schindewolf et al reported a 16.4% argatroban, 2.1% lepirudin, 23.6% danaparoid, 40 % fondaparinux treatment in a multicenter study including 195 pediatric patients with HIT and highlighted the effectiveness of off-label fondaparinux (3). The reports about anticoagulation treatment in patients with HIT under ECLS were case control studies and very limited in literature. In ECLS data, DTI therapy was especially reported in patients with HIT (1). Velagic et al (8) reported clinic recovery with fondaparinux in a 44 year old patient with ventricular assist device and Parlar et al (9) reported successful fondaparinux treatment in a postoperative patient with HIT under ECMO support after mitral valve replacement.

Fondaparinux is a pentasaccharide that selectively inhibits factor Xa by effecting anti-thrombin III (AT-III). Subcutaneous single dose of 0.1- 0.2 mg/kg daily is suggested in children. The treatment dosage should be titrated to keep anti factor Xa level in range of 0.6-1 ml/IU. Fondaparinux is not recommended in severe renal insufficiency (creatinine clearance <30), bacterial endocarditis and acute major bleeding (10,11). Side effects like bleeding, skin lesions at injection sites and deterioration of liver function tests can be seen (10).

Fondaparinux was initiated in our case as DTIs did not exist in our country.

HIT is a temporary situation and thrombocyte count can return to normal levels in a few days to few weeks. But HIT antibodies keep to circulate for weeks to few months (4,5,8). Normalization of thrombocyte count in 2-9 days by fondaparinux treatment was reported (8-10). Thrombocyte count reached to 250000/ $\mu$ L at the 6th day of the fondaparinux treatment in the presented case. The wide spread skin necrosis regressed but the right hand fingers had to be amputated up to the proximal phalanges. No side effects were determined due to the drug therapy.

In conclusion, thrombocytopenia is a frequent problem in intensive care units. Although it is a rare cause of thrombocytopenia, HIT should be kept in mind in patients treated with heparin. HIT is a difficult entity in patients with ECLS and should be treated appropriately. Fondaparinux helped to provide recovery of thrombocytopenia in this case. Extra corporeal life support could be continued for 4 more days and ceased successfully by fondaparinux anticoagulation. The patient discharged at day 48 following surgery.

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