

Heparin Resistance and Management in  
Congenital Heart Surgery: Case ReportDilek Altun<sup>1\*</sup>, Adnan Yüksek<sup>1</sup>, Ahmet Arnaz<sup>2</sup>, Yusuf Kenan Yalçınbaş<sup>3</sup> and Tayyar Sarioğlu<sup>4</sup><sup>1</sup>Acıbadem Bakırköy Hospital, Anaesthesiology and Reanimation (Cardiovascular), Bakırköy/İstanbul, Turkey<sup>2</sup>Acıbadem University, Acıbadem Bakırköy Hospital, Cardiovascular Surgery, Bakırköy/İstanbul, Turkey<sup>3</sup>Acıbadem Bakırköy Hospital, Cardiovascular Surgery, Bakırköy/İstanbul, Turkey<sup>4</sup>Acıbadem University Medical Faculty, Pediatric Cardiac Surgery, Bakırköy/İstanbul, Turkey

## Article Information

Received date: Jan 22, 2017

Accepted date: Feb 10, 2017

Published date: Feb 15, 2017

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**Keywords** Congenital heart surgery;  
Cardiopulmonary bypass; Heparin  
resistance; Activated coagulation time;  
Fresh frozen plasma

## Abstract

Anticoagulation for cardiopulmonary bypass is maintained with heparin. The primary mechanism of action of this drug is the activation of antithrombin III, which prevents thrombin transformation from prothrombin. Thus, it reduces the formation of clot. However, in some cases, despite a standard heparin dose, the intended active coagulation time cannot be obtained which is known as heparin resistance. Heparin resistance occurs in up to 22% of patients undergoing cardiac surgery requiring cardiopulmonary bypass and it is associated with decreased levels of antithrombin. Heparin resistance, although seen rare, can occur in varying severity in clinic. Treatment options for heparin resistance include administration of antithrombin or fresh frozen plasma. In this case presentation, we have reported the strategy for a planned pulmonary artery reconstruction operation under cardiopulmonary bypass in a patient that we could not maintain the adequate ACT levels despite a cumulative dose of 12 mg/kg heparin and 20 ml/kg fresh frozen plasma transfusion.

## Introduction

Adequate anticoagulation is a critical component of successful management of hemostatic and inflammatory responses associated with Cardiopulmonary Bypass (CPB). Heparin is commonly administered during CPB to achieve systemic anticoagulation [1,2]. Heparin differs pharmacokinetically from person to person and may even show different effects on the same person. Especially for children under 6 years of age, heparin resistance is often encountered depending on the reduced and variable AT activation. In addition, despite having no history of heparin and another medication use before the operation, normal thrombosis count and normal anticoagulant tests in CPB patients who receive appropriate dose of heparin, enough Active Coagulation Time (ACT) may still not be achieved and a phenomenon Heparin Resistance (HR) may encounter. In the case of development of HR, alternative treatment methods or the use of short-term effective anticoagulant agents such as lepirudin, bivalirudin and argatroban can be a potential solution to the problem [3].

## Case Report

Thirty four months old, 13.5 kg patient was admitted for reconstructive surgery. She had a previous history of pulmonary artery banding, patent ductus arteriosus ligation without CPB when she was 4 months old. There were no evidence of anticoagulant medicine use in patient's preoperative history. The patient's thrombosis count, coagulation and other laboratory tests were normal. After routine checks and 0.1 mg/kg midazolam, 2 µg/kg fentanyl, 5 mg/kg sodium-thiopental, 0.6 mg/kg rocuronium intravenous (iv) injection patient was orotracheally intubated. ACT was measured as 130 seconds before initiating CPB. For the safe aortic cannulation and a target ACT of 400 seconds and above, 4 mg/kg (400 IU/kg) heparin (Nevparin, Mustafa Nevzat, Istanbul) was administered intravenously. Four minutes after administration, ACT was measured as 239 seconds which was not satisfactory, so 1 mg/kg of heparin was added. Four minutes later satisfactory ACT was still not achieved, it was measured as 240 seconds. Additional dose of 1 mg/kg heparin was administered intravenously. Control ACT reached up to 245 seconds and twice more 2 mg/kg of heparin was added. Despite total of 10 mg/kg administered heparin, ACT duration was only 269 seconds, therefore 10 ml/kg Fresh Frozen Plasma (FFP) was added. Last value of ACT was 137 seconds, accordingly heparin flacon was changed and 2 mg/kg of additional heparin (Liquemine, Roche, Istanbul) was added. Patient was monitored with 2 different ACT devices, ACT duration was measured as 240 and 270 seconds so 10 mg/kg of FFP was given for the second time (Table 1). Because of no supply of thrombin inhibitors in our country and by taking into the consideration of the last 270 seconds ACT value, initial operation plan could no longer be carried out. Surgical plan was changed to debanding operation and it was performed without initiating CPB. After operation patient has taken to the cardiovascular intensive care unit, and was

**Table 1:** The time and amount of Heparin and FFP given before CPB; ACT levels.

Time (hr)	Amount of Heparin (mg)		ACT (sc)	FFP (ml)
	Given	Total		
09:45	-	-	130	
11:00	55	55	239	
11:15	13,5	68,5	250	
11:35	13,5	82	269	
11:55	27	109	250	
12:10	27	136	270	
12:25			237	135
12:45	27	163	240/270	
13:05			270	135

FFP: Fresh Frozen Plasma; ACT: Activated Clotting Time; CPB: Cardiopulmonary Bypass; sc: Second, hr: Hour.

\*ACT initial level

\*\*ACT level, checked with 2 different ACT device

extubated 3 hours after the operation. On the postoperative day 1 she was transferred to the cardiovascular service. There were no signs of pulmonary artery stenosis in the follow up echocardiography. One month after discharge the patients antithrombin III (AT III) value was 105% (N:80-120) and fibrinogen was 250 mg/dL (N:200-400), thrombin time was 15.9 seconds (N:14-21) which were within normal ranges. Repeated coagulation tests and platelet counts showed no abnormality. The family was informed about the patient's clinical findings related with heparin resistance and about the operation, and their consent was taken to publish this case.

## Discussion

Heparin resistance is defined as activated clotting time <400 seconds after full-dose heparinization for open heart surgery [4,5]. In this case study, standard dose of 4 mg/kg of heparin was administered before CPB but satisfactory anticoagulation was not achieved. In total 12 mg/kg (162 mg) of heparin and additional 2 doses of 10 ml/kg of FFP were administered. Although, FFP infusion and additional doses of heparin may usually be enough to reach appropriate ACT in most cases, the patient's last ACT was 270 seconds which was not enough for the cardiopulmonary bypass.

Potential risk factors for HR are old age group (65 years of age or older), thrombocyte count of more than 300 cell/mm, increased heparin clearance, previous heparin history, increase of concentration of heparin-binding proteins, increase in fibrinogen and factor VIII and lack of antithrombin (congenital and acquired) [1,2,6,7]. Our patient has none of these factors, and the coagulation tests and were normal which was checked before the operation.

Because heparin shows its effect in an indirect manner through AT, lack of AT decreases the effect of heparin thrombin inhibition. The prevalence of deficiency in congenital AT is 1/3000; AT levels in these patients are 40% to 50% less than normal rates [4-7]. In our patient AT III level one month after the operation was 105% which was within normal ranges (80-120). Thrombocytes count and other coagulation test (APTT) were also normal.

FFP and ATIII use is suggested in patients who show heparin resistance during open heart surgery [8,9]. In order to replace AT, FFP can be given to patients with lack of AT and despite high doses of heparin who show level of ACT<400 [1,10,11]. In our patient, despite repeated heparin doses and FFP, a desired anticoagulant time was not achieved and operation was completed without CPB. As a matter of fact, most congenital cardiac surgery procedures are done with the support of CPB. In such cases in which required ACT time can not be achieved and have heparin resistance, new latest anticoagulant agents suchlike, Lepirudin, Bivalirudin, Argatroban, which are short term effective, exert their effect by direct thrombin inhibition, and continuously performed by infusion can be use as an alternative to classic heparin [12-14]. Treichl et al. [12] have reported that, in patients who have developed heparin resistance despite high doses, for the purpose of prophylactic anticoagulation, argatroban would be used safely. Brian Mejak et al. [13] have reported a 6 kg patient in whom argatroban was used successfully due to heparin resistance during CPB.

Heparin resistance is an increasingly observed phenomenon hence an increased awareness by cardiothoracic clinicians and anesthesiologists is essential to ensure alternative anticoagulant strategies are rapidly considered and instituted early in such patients [5-7].

In this case study, we have reported our perioperative management of HR during pulmonary artery debanding operation. Operations with CPB, mostly 3-4 mg/kg of heparin would be sufficient for ACT levels to reach above 400 seconds. When standard dose of heparin is not enough for adequate anticoagulation which is called HR, FFP administration may ensure desired ACT time by increasing antithrombin III levels. In this case study, even with repeated heparin doses, unfortunately the necessary ACT time was not achieved and surgery was completed without CPB with alternative surgical methods. However, for the surgeries that CPB is necessary, it is crucial to have supply of thrombin inhibitors such as bivalirudin, argatroban, lepirudin in the centers which perform open heart surgeries.

There is no conflict of interest to declare as this study is not industry sponsored and we did not receive financial support for research and analysis. Signed documents declaring no conflict of interest and copyright transfer forms are enclosed.

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